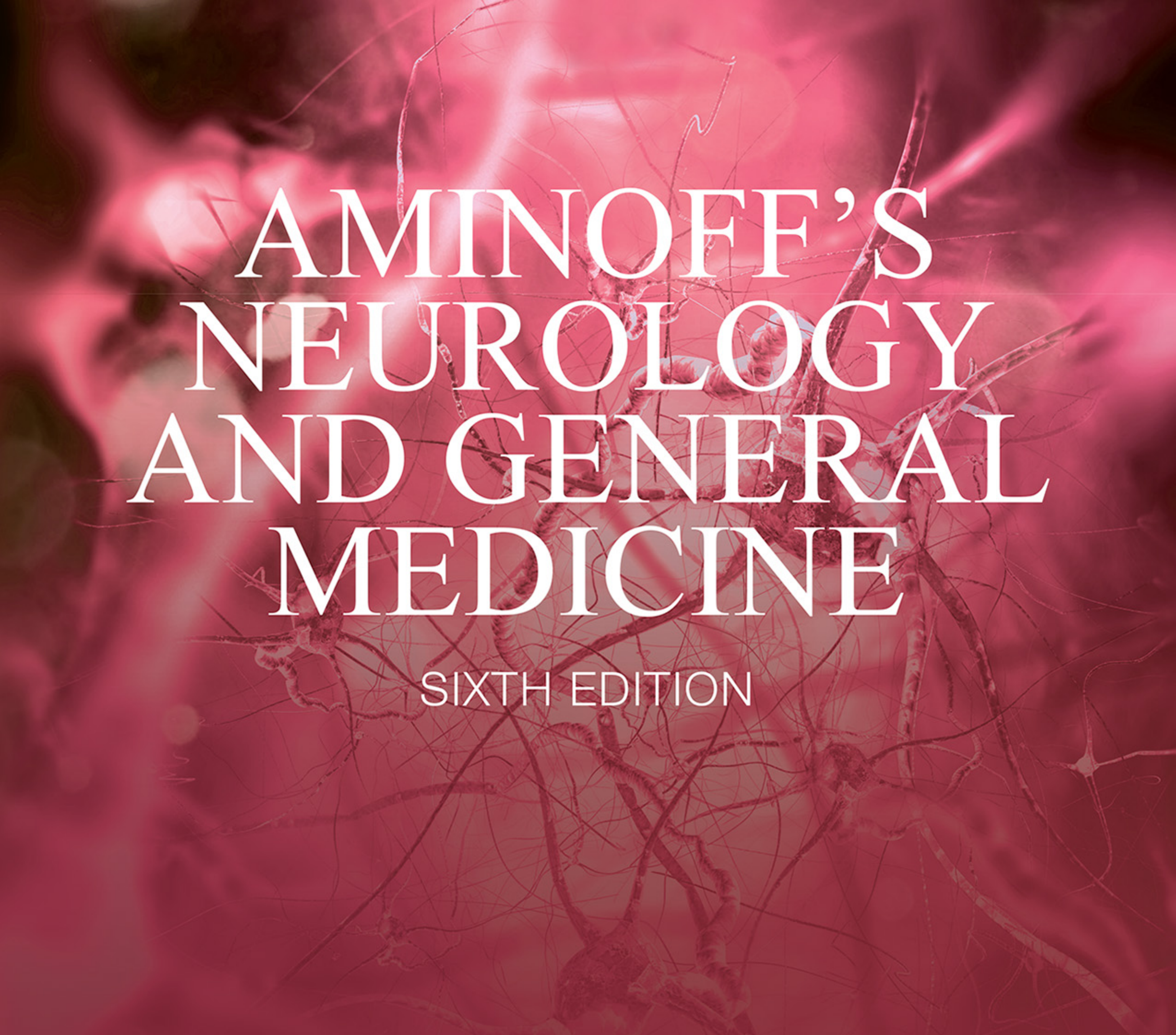

AMINOFF'S NEUROLOGY AND GENERAL MEDICINE

SIXTH EDITION

MICHAEL J. AMINOFF
S. ANDREW JOSEPHSON

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Aminoff's Neurology and General Medicine

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Aminoff's Neurology and General Medicine

SIXTH EDITION

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To the memory of
Abraham S. Aminoff,
my father and friend,

and

to my wife, Jan,
and our three children,
Alexandra, Jonathan, and Anthony
for the happiness they have brought me

Michael J. Aminoff

To my loving and supportive family,
who always provides
such happiness and joy

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Chapter 31: Pregnancy and Disorders of the Nervous System
Chapter 35: Neurotoxin Exposure in the Workplace
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Chapter 60: Neuromuscular Complications of General Medical Disorders
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Preface to the Sixth Edition

More than 30 years have elapsed since the first edition of this book was published in 1989. Over this time, clinical medicine has evolved dramatically, prompted by advances in technology and molecular biology. Many diseases have come to be understood at a more fundamental level than previously. Based on genomics and other factors, disease prediction and treatment are becoming tailored more precisely to the individual patient—so-called "personalized medicine"—as is already apparent in the management of certain cancers. It has been suggested that a simple genetic test or a cheap imaging technique may eventually make clinical consultation redundant. In the face of such complexity, however, the role of the consultant is, in some ways, more important than before. Clinical medicine is not the exact science that some imagine it to be, and doctor–patient interactions remain as important as ever.

Recent advances and a daunting expansion of the published literature have led to increasing specialization and subspecialization in every branch of medicine, and it is more difficult than ever for physicians to keep abreast of developments in more than their own field. Nevertheless, specialists need to know when to collaborate and communicate with other specialists, and thus require a good fund of general medical knowledge and the ability to recognize what they do not know.

Earlier editions of this book received a wide and generous acceptance, but the changes that have occurred in the field in the last few years have emphasized the need for a new edition. The aim of the book, however, remains the same as previously—to define both the neurologic aspects of general medical disorders and the general medical and other implications of various neurologic diseases. The book therefore provides an account of clinical neurology from a different perspective than many other textbooks and serves as an interface between neurology and the other medical specialties. This interface is important. Many patients with neurologic disorders are elderly and inevitably have other co-existing disorders. Furthermore, many medical disorders have neurologic complications or manifestations. Thus, gluten sensitivity, for example, may have both neurologic and gastrointestinal consequences, and a stroke may occur as a complication of cardiac, infective, inflammatory, or hematologic disorders. Moreover, the treatment of a general medical disorder may have neurologic consequences, as exemplified by the peripheral neuropathy that may follow the use of certain drugs. General medical disorders, in turn, are influenced by neurologic disease, as when the inability to wean a critically ill patient from a ventilator reflects an underlying critical illness neuropathy, and respiratory tract infections may affect the management of diverse neurologic diseases such as myasthenia gravis, multiple sclerosis, and epilepsy.

We hope that the contents of the book will be helpful to all clinicians, but the volume is aimed especially at neurologists, internists, hospitalists, and primary healthcare providers. We believe that it will help neurologists to appreciate the implications of the general medical issues facing their patients and how these might best be managed, and that it will aid internists, family practitioners, and other physicians to gain further understanding of their patients' neurologic disorders and thereby improve patient care. It should appeal to both junior and senior physicians, serving as a guide to the former as they complete their training and hone their clinical skills, and as a reference work summarizing clinical developments and advances for more experienced physicians, who must engage in lifelong learning in order to maintain the highest standards of clinical care.

We are grateful to our contributors, acknowledged experts in their respective fields, for taking the time to update and—in some cases—extensively rewrite their chapters or provide a completely new offering. Some have contributed to the book from its very inception or for several editions, while others are more recent or new contributors. All of them have been most gracious and patient with us as we reminded them of deadlines and made various requests of them. Inevitably time has taken its toll and some of our previous authors have had to be replaced because of retirement or ill-health. We appreciate all their past support in making this book a valued contribution to the medical literature, thank them for their contributions, and wish them well.

In preparing the present edition, one of the most difficult decisions that we made was to limit the size of the bibliography of individual chapters in order to keep the book to a manageable size. Beliefs or observations once challenged but now incorporated into the general body of knowledge do not need referencing. For those of our readers requiring more detailed bibliographic information, however, references to the older literature are provided in earlier editions of this book and new work is readily found on the Internet. In addition to appearing in print form, the book is also published electronically, which should make it more easily and widely accessible and facilitate searches for specific information.

As in the past, our families provided constant support and encouragement as we saw the book through to publication, and we are indebted to them. As mentioned in the prefaces to earlier editions, this book has particular family significance to one of us (MJA). My wife, Jan, shouldered many extra burdens to ensure that I had time to work uninterrupted on this new edition, and I cannot thank her enough for her love, help, and support. When the first edition was published in 1989, our children were in school or preschool. They have grown up with the book. Alexandra, our eldest, is now a pediatric rheumatologist at the Kaiser Permanente Oakland Medical Center. I have gained much in discussing clinical cases with her, and she has been wonderful in helping my wife and I as we sheltered in place during the COVID-19 pandemic that began while this volume was in production. Our two sons are lawyers—Jonathan is a federal defense attorney in Los Angeles, while Anthony is a trial attorney in the criminal division at the Department of Justice in Washington, DC. I have enjoyed debating issues with them and delight in their enthusiasm and intellectual prowess. Throughout the pandemic, our family has held regular zoom meetings that are the highlight of our week and through which the progress of the book has been followed.

We are grateful to a number of people at Elsevier, our publisher, for their help and especially to Ms. Melanie Tucker and Ms. Tracy Tufaga for unfailing assistance in the development of this book, and to Ms. Kiruthika Govindaraju, project manager, for seeing the volume through the production process. Some of the illustrations in the book are taken from previously published sources, as is acknowledged in the figure legends, and we are grateful for permission to reproduce them here.

Michael J. Aminoff MD, DSc, FRCP
S. Andrew Josephson MD

Preface to the First Edition

The increasing sophistication and complexity of modern medicine have led to greater specialization among practitioners and to more restricted communication between physicians in different disciplines. Perhaps, inevitably, this trend has created certain major problems. These difficulties are particularly well exemplified by the relationship between neurology and general medicine.

For non-neurologists, evaluation of patients with neurologic symptoms and signs has always been difficult because of the complexity of the anatomy and physiology of the nervous system and frustrating because the therapeutic options have seemed somewhat limited. Nevertheless, a number of neurologic diseases are exacerbated by, or occur as specific complications of, general medical disorders. Appropriate management of these neurologic disturbances requires their early recognition and an appreciation of their prognosis. It is equally important to recognize the manner in which such neurologic disorders may influence the management of the primary or co-existing medical condition, as well as the manner in which systemic complications of neurologic disorders may require somewhat different management than when these complications occur in other settings.

For neurologists, who are being asked increasingly to evaluate neurologic disturbances presenting in the context of other medical disorders, the difficulty is equally apparent. The general background of cases is frequently confusing, the relationship of the neurologic to the other medical problems is commonly not appreciated, and the manner in which treatment needs to be “tailored” to the specific clinical context is often not clear. Furthermore, neurologic disturbances may themselves be the presenting feature of general medical disorders or lead to general medical complications requiring speedy recognition and effective management.

I hope that the present volume will appeal to both neurologists and physicians in other specialties by providing a guide to the neurologic aspects of general medical disorders and to some of the medical complications of certain neurologic diseases. It is not intended to be a textbook of neurology, but rather a “bridge” between neurology and the other medical specialties.

It is a pleasure to acknowledge the help that I received from various people in developing this book. I am grateful to the various contributors, who devoted a great deal of time and energy to reviewing developments in their own fields of interest and showed considerable tolerance of the many demands that I made upon them. I am grateful also to Mr. Robert Hurley and Ms. Margot Otway at Churchill Livingstone for their help and advice during the preparation of this book. Finally, the support and encouragement of my wife, Jan, and of our children, Alexandra, Jonathan, and Anthony, did much to ease the burden involved in seeing this volume to its conclusion.

Michael J. Aminoff MD, DSc, FRCP

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Contents

Section 1 Respiratory and Cardiovascular Disorders

1. Breathing and the Nervous System 3
Shweta Prasad, Pramod Kumar Pal and Robert Chen

2. Neurologic Complications of Aortic Disease and Surgery 21
Douglas S. Goodin

3. Neurologic Complications of Cardiac Surgery 43
Maulik P. Shah

4. Neurologic Complications of Congenital Heart Disease and Cardiac Surgery in Children 53
Shabnam Peyvandi, Christine Fox and Kendall Nash

5. Neurologic Manifestations of Acquired Cardiac Disease and Arrhythmias 65
Ryan T. Muir and David J. Gladstone

6. Neurologic Manifestations of Infective Endocarditis 87
Steven M. Phillips and Linda S. Williams

7. Neurologic Complications of Hypertension 101
Anthony S. Kim

8. Dysautonomia, Postural Hypotension, and Syncope 123
Michael J. Aminoff

9. Neurologic Complications of Cardiac Arrest 147
Vanja C. Douglas

10. Cardiac Manifestations of Acute Neurologic Lesions 157
Chung-Huan Sun and Nerissa U. Ko

11. Stroke as a Complication of General Medical Disorders 171
Lironn Kraler and Gregory W. Albers

Section 2 Gastrointestinal Tract and Related Disorders

12. Hepatic and Pancreatic Encephalopathy 191
Karin Weissenborn

13. Other Neurologic Disorders Associated with Gastrointestinal Disease 201
Delaram Safarpour, Kaveh Sharzehi and Ronald F. Pfeiffer

14. Disturbances of Gastrointestinal Motility and the Nervous System 217
Michael Camilleri

15. Neurologic Manifestations of Nutritional Disorders 235
Brent P. Goodman

Section 3 Renal and Electrolyte Disorders

16. Neurologic Dysfunction and Kidney Disease 251
Michael J. Aminoff

17. Neurologic Complications of Electrolyte Disturbances 273
Amar Dhand

Section 4 Endocrine Disorders

18. Thyroid Disease and the Nervous System 285
Nick Verber and Pamela J. Shaw

19. Diabetes and the Nervous System 303
Kaylynn Purdy and Douglas W. Zochodne

20. Sex Hormone, Pituitary, Parathyroid, and Adrenal Disorders and the Nervous System 317
Hyman M. Schipper and Gary M. Abrams

Section 5 Cutaneous Disorders

21. The Skin and Neurologic Disease 343
Orest Hurko

Section 6 Bone and Joint Disease

22. Neurologic Disorders Associated with Bone and Joint Disease 373
Ann Noelle Poncelet and Andrew P. Rose-Innes

Section 7 The Ears, Eyes, and Related Systems

23. Otoneurologic Manifestations of Otologic and Systemic Disease 399
Joseph M. Furman and Andrew A. McCall

24. Neuro-Ophthalmology in Medicine 415
Sashank Prasad

Section 8 Hematologic and Neoplastic Disease

25. Neurologic Manifestations of Hematologic Disorders 441
J.D. Sussman and G.A.B. Davies-Jones

26. Metastatic Disease and the Nervous System 475
Jasmin Jo and David Schiff

27. Paraneoplastic and Nonparaneoplastic Autoimmune Syndromes of the Nervous System 499
Sarosh R. Irani

28. Neurologic Complications of Chemotherapy and Radiation Therapy 521
Thomas J. Kaley and Lisa M. DeAngelis

Section 9 Genitourinary System and Pregnancy

29. Lower Urinary Tract Dysfunction and the Nervous System 541
Amit Batla and Jalesh N. Panicker

30. Sexual Dysfunction in Patients with Neurologic Disorders 557
David B. Vodušek and Michael J. Aminoff

31. Pregnancy and Disorders of the Nervous System 577
Michael J. Aminoff

Section 10 Toxic, Environmental, and Traumatic Disorders

32. Drug-Induced Disorders of the Nervous System 603
Frank L. Mastaglia

33. Alcohol and the Nervous System 627
Robert O. Messing

34. Neurologic Complications of Recreational Drugs 637
S. Andrew Josephson

35. Neurotoxin Exposure in the Workplace 647
Michael J. Aminoff

36. Abnormalities of Thermal Regulation and the Nervous System 661
Douglas J. Gelb

37. Concussion 673
Cathra Halabi

Section 11 Infections, Inflammatory, and Immunologic Disorders

38. Acute Bacterial Infections of the Central Nervous System 683
Kyle J. Coleman and Karen L. Roos

39. Spirochetal Infections of the Nervous System 703
John J. Halperin

40. Tuberculosis of the Central Nervous System 717
John M. Leonard

41. Leprosy 727
Winnie W. Ooi and Jayashri Srinivasan

42. Nervous System Complications of Systemic Viral Infections 741
John E. Greenlee

43. HIV and Other Retroviral Infections of the Nervous System 765
Michael J. Peluso and Serena Spudich

44. Neurologic Complications of Transplantation and Immunosuppressive Agents 785
Alexandra D. Muccilli, Elan Guterman and S. Andrew Josephson

45. Fungal Infections of the Central Nervous System 803
John R. Perfect

46. Parasitic Infections of the Central Nervous System 821
Anita A. Koshy

47. Chronic Meningitis 839
Prashanth S. Ramachandran and Michael R. Wilson

48. Neurologic Complications of Vaccination 853
Augusto Miravalle

49. Sarcoidosis of the Nervous System 867
Olwen C. Murphy, Allan Krumholz and Barney J. Stern

50. Connective Tissue Diseases, Vasculitis, and the Nervous System 885
John C. Probasco

Section 12 Sleep and Its Disorders

51. Neurologic Aspects of Sleep Medicine 911
Renee Monderer, Shelby Harris and Michael Thorpy

Section 13 Psychogenic Disorders

52. Functional (Psychogenic) Neurologic Disorders 941
Carine W. Maurer and Mark Hallett

Section 14 Imaging and Perioperative Care

53. Neurologic Complications of Imaging Procedures 951
William P. Dillon and Matthew R. Amans

54. Preoperative and Postoperative Care of Patients With Neurologic Disorders 965
John P. Betjemann and S. Andrew Josephson

55. Neurologic Disorders and Anesthesia 979
Alejandro A. Rabinstein

Section 15 Critical Illness and General Medical Disorders

56. Neurologic Complications in Critically Ill Patients 993
John A. Morren and Edward M. Manno

57. Seizures and General Medical Disorders 1007
Simon M. Glynn and Jack M. Parent

58. Movement Disorders Associated With General Medical Diseases 1023
Michael J. Aminoff and Chadwick W. Christine

59. Headache in General Medical Conditions 1047
Morris Levin

60. Neuromuscular Complications of General Medical Disorders 1057
Jeffrey W. Ralph and Michael J. Aminoff

61. Disorders of Consciousness in Systemic Diseases 1085
J. Claude Hemphill

62. Dementia and Systemic Disease 1099
Vanja C. Douglas and S. Andrew Josephson

63. Care at the End of Life 1111
Michael J. Aminoff

Index 1123

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SECTION

1

Respiratory and Cardiovascular Disorders

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CHAPTER

1

Breathing and the Nervous System

SHWETA PRASAD ■ PRAMOD KUMAR PAL ■ ROBERT CHEN

PHYSIOLOGY OF BREATHING
- Respiratory Rhythm Pattern Generators
- Control of Breathing
  - *Chemical Control of Breathing*
  - *Mechanical Inputs from Airways, Lungs, and Chest Wall*
  - *Voluntary Control of Breathing*
- Factors Influencing the Control of Breathing
  - *Sleep*
  - *Cerebrovascular Responsiveness*
  - *Age*
  - *Sex*
  - *Genetic Factors*

EVALUATION OF PULMONARY FUNCTION
- Clinical Assessment
- Tests of Pulmonary Function
  - *Pulmonary Function Tests*
  - *Arterial Blood Gas Studies*
  - *Imaging*
  - *Polysomnography*

PATTERNS OF RESPIRATORY DYSFUNCTION
- Central Nervous System Lesions
  - *Cheyne—Stokes Breathing*
  - *Hyperpnea*
  - *Apneustic Breathing*
  - *Ataxic Breathing*
- Disorders of Involuntary Respiratory Control
  - *Congenital Central Hypoventilation Syndrome*
  - *Acquired Central Hypoventilation*
- Disorders of Voluntary Respiratory Control
- Miscellaneous Disorders
  - *Central Neurogenic Hyperventilation*
  - *Posthyperventilation Apnea*
  - *Apraxia of Breathing*
  - *Cluster Breathing*
  - *Hiccup*
  - *Sneezing and Yawning*
  - *Diaphragmatic Myoclonus*

RESPIRATORY DYSFUNCTION FROM NEUROLOGIC DISORDERS
- Stroke
- Movement Disorders
  - *Hypokinetic Disorders*
  - *Hyperkinetic Disorders*
- Demyelinating Disorders
- Neuromuscular Disorders
  - *Anterior Horn Cell Disorders*
  - *Neuropathies*
  - *Neuromuscular Junction Disorders*
  - *Myopathies*
- Spinal Cord Lesions
  - *Cervical Spinal Cord Injury*
  - *Thoracic Cord Injury*
- Miscellaneous Disorders
  - *Epilepsy*
  - *Brain Tumors*

DISORDERS OF BREATHING ASSOCIATED WITH SLEEP
- Upper Airway Obstruction
- Central Sleep Apnea Syndromes
- Sleep Hypoventilation Syndrome
- Respiratory Dysrhythmias
- Sudden Infant Death Syndrome

NEUROLOGIC EFFECTS OF RESPIRATORY DYSFUNCTION
- Dysfunction Related to Pulmonary Pathology
  - *Hypoxia*
  - *Hypercapnia*
- Dysfunction Related to Obstructive Sleep Apnea
  - *Vascular Disorders*
  - *Cognitive Dysfunction*
  - *Headache*
  - *Epilepsy*

CONCLUDING COMMENTS

Respiration involves pulmonary ventilation, gaseous exchange between lung alveoli and blood, and transport of oxygen and carbon dioxide between the blood, tissues, and interstitial fluids. The nervous system plays a pivotal role in controlling pulmonary ventilation as it exerts both automatic and

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voluntary control over breathing. The anatomic pathways involve the cerebral hemispheres, pons, medulla, spinal cord, anterior horn cells, nerves, and neuromuscular junctions, as well as peripheral chemoreceptors and lung mechanoreceptors and the respiratory muscles themselves. Several central and peripheral neurologic disorders can affect respiration adversely, and hypoxia and hypercapnia resulting from respiratory dysfunction may affect the nervous system and produce neurologic complications.

PHYSIOLOGY OF BREATHING

Breathing is a predominantly involuntary, rhythmic phenomenon that can be overridden by voluntary control. Although the pathways for automatic and voluntary breathing are anatomically separate, they demonstrate significant functional integration (Fig. 1-1).

Respiratory Rhythm Pattern Generators

The respiratory rhythm originates in the medulla and neuronal activity in the brainstem can be divided into inspiratory, postinspiratory, and preinspiratory (or late expiratory) neural activities. Two main groups of neurons in the medulla are implicated in the regulation of respiration, namely the dorsal respiratory group (DRG) and the ventral respiratory group (VRG). The DRG is thought to be activated prior to inspiration, and the VRG is considered to modulate expiration. *N*-methyl-D-aspartate (NMDA) receptors are the major mediators of VRG ventilatory drive, with modulation by non-NMDA glutamate systems. In addition, recent studies have identified several other respiratory pattern generators (RPGs) in the medulla.[1] Among these, the pre-Bötzinger complex is considered to be the primary RPG that provides the inspiratory rhythm, and the retrotrapezoid nucleus and parafacial respiratory group, which contain chemosensitive neurons, are thought to provide rhythmic expiratory drive by producing tonic excitation to the pre-Bötzinger and Bötzinger complexes. In addition, located rostrally in the pons, the pneumotaxic center, comprised of the Kölliker-Fuse and parabrachial nuclei, are suggested to be the relay nuclei for reflex and higher-order control of breathing. The Kölliker-Fuse nuclei are also crucial for transition from inspiration to expiration and for modulation of airway patency during breathing. Overall, respiratory rhythm generation is controlled by multiple factors including noradrenergic, serotonergic, peptidergic, and cholinergic neurons.

Control of Breathing

The control of breathing occurs at multiple levels of the respiratory system through a negative feedback system that ensures precise control of arterial PO_2, PCO_2, and pH.[1] This homeostasis is maintained by an integration of chemical, metabolic, and mechanical inputs and adjusting the ventilatory output to meet the metabolic demands (Fig. 1-1).

CHEMICAL CONTROL OF BREATHING

Peripheral and central chemoreceptors monitor afferent inputs (arterial PO_2 and PCO_2). The central chemoreceptors modulate respiration based on changes in CO_2/pH detected in the brain, whereas the peripheral chemoreceptors, which act faster, sense changes in the periphery.

Central chemoreceptor sites are responsible for approximately two-thirds of the ventilatory response to CO_2/pH. Eight major central chemoreceptor sites have been reported and these are distributed throughout the lower brainstem.[1] Peripheral chemoreceptors are located in the carotid body, bifurcation of the carotid artery, and the arch of the aorta. The carotid bodies are the major chemoreceptor sites for hypoxia and are very sensitive to changes in partial pressure of arterial oxygen (PaO_2), arterial carbon dioxide ($PaCO_2$), and H^+. Peripheral and central chemoreceptors are anatomically linked, and this interdependence determines the normal respiratory drive in eupneic and hypoxic conditions. Carotid bodies have been shown to exert a tonic drive on the output of central chemoreceptors, and the magnitude of sensory input from the carotid chemoreceptor is known to influence the central chemoreceptor response.

MECHANICAL INPUTS FROM AIRWAYS, LUNGS, AND CHEST WALL

Inputs from the chest wall and respiratory muscles predominantly affect the pattern of breathing and are most evident when there is an increased

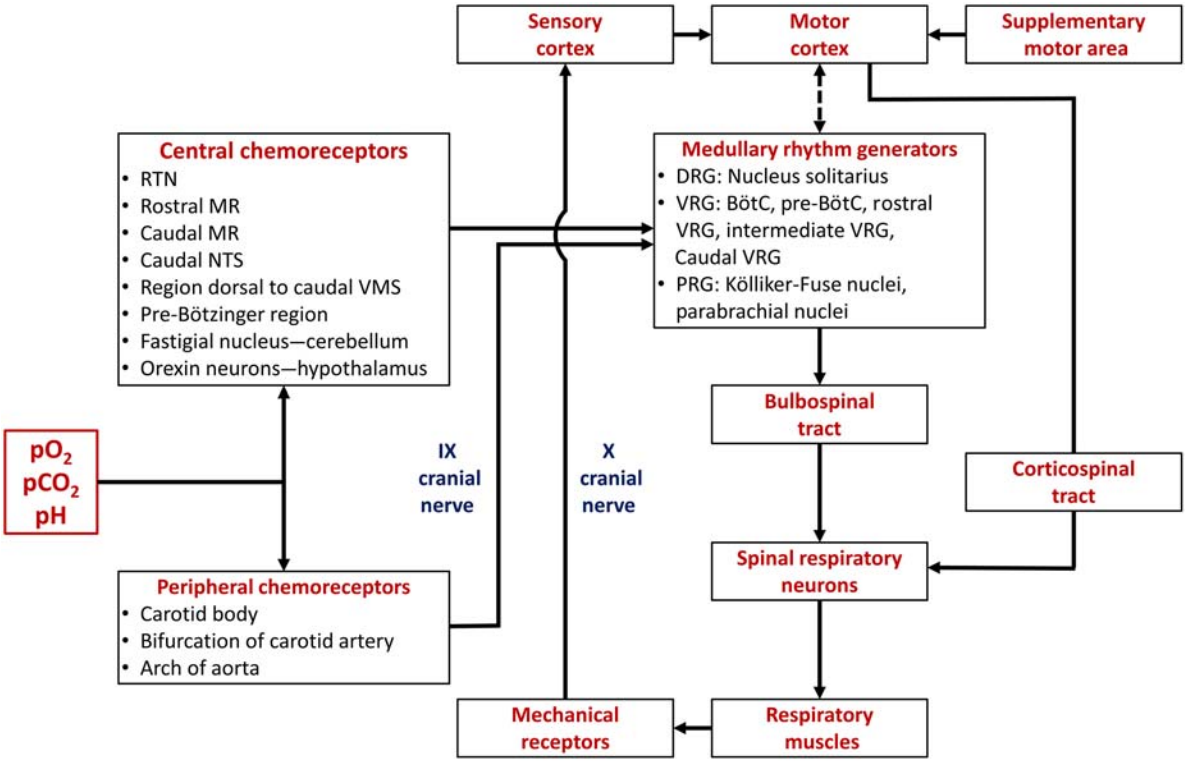
Sensory cortex
Motor cortex
Supplementary motor area
Central chemoreceptors
• RTN
• Rostral MR
• Caudal MR
• Caudal NTS
• Region dorsal to caudal VMS
• Pre-Bötzinger region
• Fastigial nucleus—cerebellum
• Orexin neurons—hypothalamus
Medullary rhythm generators
• DRG: Nucleus solitarius
• VRG: BötC, pre-BötC, rostral VRG, intermediate VRG, Caudal VRG
• PRG: Kölliker-Fuse nuclei, parabrachial nuclei
pO2 pCO2 pH
IX cranial nerve
X cranial nerve
Bulbospinal tract
Corticospinal tract
Spinal respiratory neurons
Peripheral chemoreceptors
• Carotid body
• Bifurcation of carotid artery
• Arch of aorta
Mechanical receptors
Respiratory muscles

FIGURE 1-1 ■ Schematic representation of neural control of breathing. BötC, Bötzinger complex; DRG, dorsal respiratory group; MR, medullary raphe; NTS, nucleus of tractus solitarius; PRG, pontine respiratory group; RTN, retrotrapezoid nucleus; VMS, ventral medullary surface; VRG, ventral respiratory group.

ventilatory demand. Respiratory muscles play a significant role in respiration by aiding in the expansion and contraction of the thoracic cavity. The main inspiratory muscles include the diaphragm, external intercostal and scalene muscles, with accessory inspiratory muscles being the sternocleidomastoid, pectoralis major and minor, serratus anterior, latissimus dorsi, and serratus posterior superior. The expiratory muscles are the internal intercostals, external oblique, internal oblique, rectus abdominis, transverse abdominis, and serratus posterior inferior. Muscles of the upper airway do not have a direct action on the chest cage or intrathoracic volume, but are crucial to keep the airway open during inspiration, regulate airway resistance, and partition airflow through nasal and oral pathways. These are muscles of the soft palate, pharynx, larynx, trachea, nose, and mouth, and are innervated by cranial nerves V, VII, IX, X, and XII. At the level of airways, the Hering–Breuer reflex, which is elicited by inflation of slow-adapting pulmonary stretch receptors, causes inhibition of inspiratory effort following stretching of the airway. In addition, the laryngeal chemoreflex, which produces reflexive central apnea, bradycardia, and glottis closure on exposure of the laryngeal mucosa to acidic or organic stimuli, plays a protective role. However, this reflex has been considered to play a role in the pathogenesis of sudden infant death syndrome.[1]

VOLUNTARY CONTROL OF BREATHING

Voluntary control of breathing is mediated by the descending corticospinal tract and its influence on the motor neurons innervating the diaphragm and intercostal muscles. The rate and rhythm of breathing are influenced by the forebrain, as observed during voluntary hyperventilation or breath-holding, as well as during the semivoluntary or involuntary rhythmic alterations in ventilatory pattern that are required during speech, singing, laughing, and crying.

Electrophysiologic and imaging studies have shown that specific areas of cortex are involved in different phases of voluntary breathing. The diaphragm can be activated by stimulation of the contralateral motor cortex using transcranial magnetic stimulation. The diaphragm lacks significant bilateral cortical representation, consistent with the finding of attenuation of diaphragmatic excursion only on the hemiplegic side in patients with hemispheric stroke, and intercostal muscles are similarly affected by hemispheric lesions. Positron emission tomographic studies have shown an increase in cerebral blood flow in the primary motor cortex bilaterally, the right supplementary motor cortex, and the ventrolateral thalamus during inspiration; and the same structures, along with the cerebellum, are involved in expiration.

The involvement of the forebrain in the regulation of breathing is further substantiated by the induction of apnea that follows stimulation of the anterior portion of the hippocampal gyrus, the ventral and medial surfaces of the temporal lobe, and the anterior portion of the insula.

Factors Influencing the Control of Breathing

Several factors including but not limited to sleep, cerebrovascular responsiveness, age, sex, and genetic factors influence the control of breathing.[1]

Sleep

During sleep, owing to the loss of wakefulness stimuli, breathing is entirely dependent on stimuli from chemoreceptors and mechanoreceptors. Transient central apnea and breathing instability can frequently occur during the transition from wakefulness to sleep. During nonrapid eye movement (NREM) sleep, loss of the wakefulness drive to breathe renders respiration highly dependent on metabolic and chemical influences, particularly $PaCO_2$. During REM sleep, respiratory control is insensitive to changes in $PaCO_2$, and is predominantly under behavioral control. Owing to this, central sleep apnea (CSA) is relatively uncommon in REM compared to NREM sleep. Due to the increased ventilatory motor output and reduced chemosensitivity, the hypercapnic and hypoxic ventilatory drive are blunted in REM sleep.

Cerebrovascular Responsiveness

Cerebrovascular responsiveness to CO_2 is a crucial determinant of hypercapnic ventilatory response and eupneic ventilation. A reduction in cerebral blood flow results in accumulation of CO_2 which stimulates the medulla, whereas an increase in blood flow depresses ventilation owing to a rapid removal of CO_2. Hence, alteration in blood flow lead to variations in cerebrovascular responsiveness to CO_2 which may contribute to respiratory abnormalities.

Age

Older adults are more prone to sleep apnea because cerebral blood flow regulation and cerebrovascular responsiveness are reduced in them, and sleep state oscillations may precipitate apnea. Transient instability in breathing and central apnea may often occur during transitions from wakefulness to NREM sleep. As sleep oscillates between the above-mentioned states, $PaCO_2$ is at or below the apneic threshold, that is, the level required to maintain rhythmic ventilation during sleep, and this results in central apnea. Recovery from this is associated with transient hyperventilation and wakefulness.

Sex

Experimental evidence has suggested a role of sex hormones in alteration of the hypocapnic apneic threshold during sleep, and women have been reported to be less susceptible than men to develop hypocapnic central apnea during NREM sleep.

Genetic Factors

A significant number of transcription factors are known to play a role in the control of breathing. The most clinically relevant is the *PHOX2B*, which is involved in the development of the retrotrapezoid nucleus, and mutations of this gene have been documented to produce congenital central hypoventilation syndrome.[1]

EVALUATION OF PULMONARY FUNCTION

A detailed discussion of the evaluation of pulmonary function is beyond the scope of this chapter.

The following is a summary of an approach to evaluating patients with impaired breathing in the setting of neurologic illness. The onset, distribution, character, and accompaniments of weakness may suggest the underlying cause. History obtained from a bed-partner or caregiver is important in determining the presence of sleep-disordered breathing.

Clinical Assessment

A detailed clinical history should be obtained and importance paid to any history of breathing or cardiac problems. The time of onset and temporal relationship to neurologic symptoms should be ascertained. Furthermore, the presence of any illness (such as infections) that may have preceded the onset of muscle weakness (e.g., in Guillain–Barré syndrome) should be recorded.

The respiratory and cardiac systems are examined to determine the respiratory rate and volume, pattern of breathing, heart rate, blood pressure, temperature, and presence of cyanosis. Bedside assessments should also include a single-breath counting exercise, observation of chest expansion, and testing of cough strength. Diaphragmatic weakness may give rise to paradoxical inward movement of the abdomen during inspiration. The presence of hypophonia, nasal intonation, dysarthria, dysphagia, and pooling of secretions suggest bulbar dysfunction. Auscultation of the chest may reveal features of bronchoconstriction, pulmonary congestion, or consolidation.

Tests of Pulmonary Function

Pulmonary Function Tests

Pulmonary function tests can be used to provide quantitative information about pulmonary function. Bedside spirometry is useful to assess pulmonary function, especially in neuromuscular disorders. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and maximal inspiratory force (MIF) should be measured.[2] In neuromuscular disorders, a “restrictive” pattern of respiratory dysfunction is seen, evidenced by a normal or sometimes higher ratio of FEV1 to FVC. MIF is an indicator of the strength of the respiratory muscles.

Arterial Blood Gas Studies

Arterial blood gas analysis (pH, $PaCO_2$, PaO_2) is required for patients with impending respiratory failure to determine the need for ventilatory support. Overnight pulse oximetry is useful in patients with sleep-related breathing problems.

Imaging

Imaging plays a major role in the assessment of pulmonary function and diseases. Although a wide range of imaging techniques are available, computed tomography (CT) is still the mainstay of imaging as it allows high-resolution and quick assessment of the lung parenchyma and its surrounding structures. A CT scan of the thorax may sometimes be useful to detect small pleural effusions as well as mediastinal masses and lymphadenopathy. Functional imaging of the diaphragm using fluoroscopy or ultrasound is undertaken to evaluate diaphragmatic dysfunction, specifically diaphragmatic weakness secondary to phrenic nerve palsy.

Polysomnography

Polysomnography is useful to study abnormalities of breathing during different stages of sleep. Breathing is monitored by recording the airflow at the nose and mouth using thermal sensors and a nasal pressure transducer, effort is recorded using inductance plethysmography, and oxygen saturation is also measured. The breathing pattern is analyzed for the presence of apneas and hypopneas.

PATTERNS OF RESPIRATORY DYSFUNCTION

Disorders of the peripheral and central nervous system (CNS) may result in respiratory insufficiency through different mechanisms. The pattern of respiratory dysfunction primarily depends on the site of the lesion rather than the underlying etiology, whereas prognosis depends on both factors. Weakness of respiratory muscles may result in a restrictive pattern of ventilatory insufficiency. Oropharyngeal and laryngeal weakness can result in an obstructive pattern, especially during sleep. Patients with neuromuscular diseases and bulbar involvement are at risk of recurrent aspiration pneumonia and acute upper airway obstruction.

Central Nervous System Lesions

As discussed in an earlier section, the neurons responsible for generation of respiratory rhythm are located in the medulla, and their output to respiratory muscles through the reticulospinal tract is modulated by chemical and neural afferents. Specific breathing patterns have been reported in neurologic diseases based on the site of lesion.[3]

CHEYNE–STOKES BREATHING

Cheyne–Stokes breathing is characterized by a cyclical escalation of hyperventilation followed by decremental hypoventilation and finally apnea (Fig. 1-2). In humans, cycle lengths from 40 to 100 seconds may occur. During Cheyne–Stokes breathing, analysis of arterial blood gases shows cyclical variations. In the hyperventilation stage, there is a decrease in PaO_2 and pH and an increase in $PaCO_2$, which is followed by an increase in PaO_2 and pH, and a declining $PaCO_2$ during the decremental hypoventilation phase. This pattern may be observed with bilateral cortical or diencephalic dysfunction caused by either structural damage or metabolic problems. It can also occur in patients with cardiac failure and in most normal individuals while sleeping at high altitudes.

HYPERPNEA

Hyperpnea or hyperventilation with regular deep breaths is indicative of a CNS lesion in rare instances. It is more often observed in patients with underlying medical conditions including sepsis and liver failure.

APNEUSTIC BREATHING

This is a pattern characterized by prominent, prolonged end-inspiratory pauses (Fig. 1-2) and is observed in lesions of rostral pons that involve the pneumotaxic center, that is, the Kölliker-Fuse–parabrachial complex.

ATAXIC BREATHING

Ataxic or irregular breathing is a pattern of breaths that are irregular in duration, frequency, and depth (Fig. 1-2). This pattern is usually observed with lesions of the pontomedullary junction and frequently heralds the onset of respiratory failure.

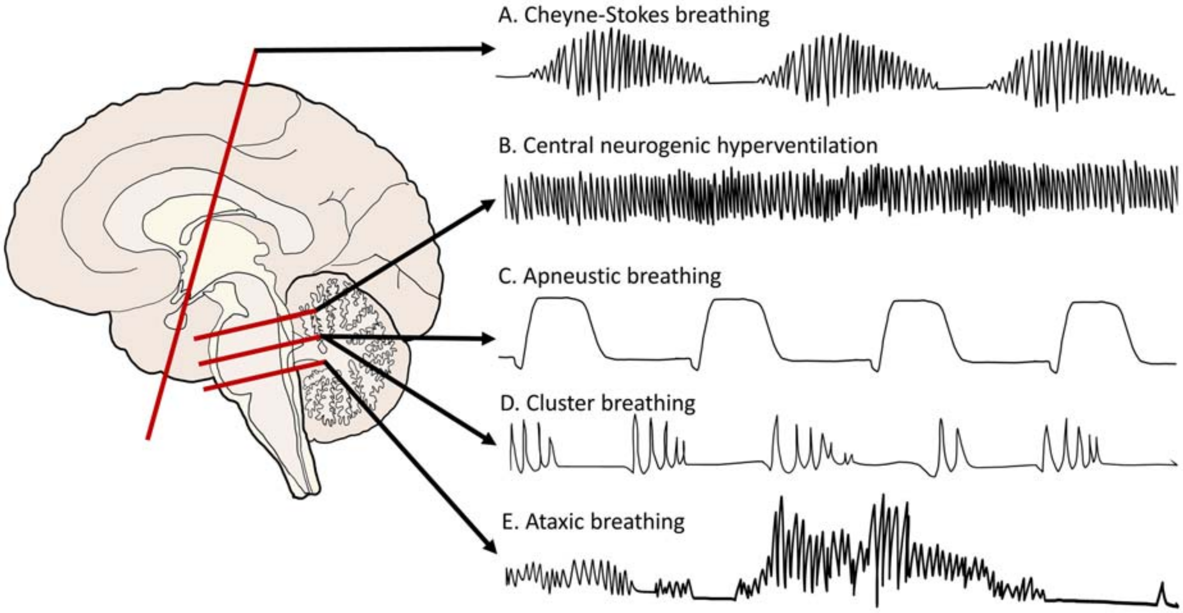
A. Cheyne-Stokes breathing
B. Central neurogenic hyperventilation
C. Apneustic breathing
D. Cluster breathing
E. Ataxic breathing

FIGURE 1-2 ■ Abnormal patterns of respiration.

Disorders of Involuntary Respiratory Control

CONGENITAL CENTRAL HYPOVENTILATION SYNDROME

Congenital central hypoventilation (Ondine curse) is a rare disorder characterized by intact volitional breathing with the inability to maintain respiration during sleep.[3] Patients experience apnea or hypopnea during sleep, most often during NREM sleep. Mutations of the *PHOX2B* gene have been implicated in this autosomal dominant disease.[1]

ACQUIRED CENTRAL HYPOVENTILATION

A phenomenology similar to congenital central hypoventilation syndrome has been described in bilateral or unilateral medullary infarction, bulbar poliomyelitis, neurodegenerative disorders such as multiple system atrophy (MSA), syringobulbia, paraneoplastic brainstem syndromes, and idiopathic sleep apnea.[3] Iatrogenic injury has been reported following bilateral cervical tractotomy performed for intractable pain, presumably as a result of damage to the descending reticulospinal tracts which activate phrenic motor neurons and the ascending spinoreticular fibers that carry afferent information to brainstem centers.

Disorders of Voluntary Respiratory Control

The relatively pure form of voluntary breathing dysfunction is observed in the “locked-in” syndrome,[3] wherein patients are unable to voluntarily control breathing and cannot speak, but have a regular ventilatory pattern, preserved response to CO_2 stimulation, and experience air hunger. Mid-pontine lesions are usually responsible and may be due to infarctions, hemorrhage, myelinosis, or tumors, which result in disruption of the corticospinal and corticobulbar fibers that control voluntary respiration while sparing the medullary respiratory centers that control automatic ventilation. Disordered voluntary breathing may also be observed in extrapyramidal and cerebellar disorders, to be discussed later.

Miscellaneous Disorders

CENTRAL NEUROGENIC HYPERVENTILATION

This is an abnormal pattern of breathing characterized by deep and rapid breaths of at least 25 breaths per minute (Fig. 1-2). Although central neurogenic hyperventilation was thought to be a classic and specific manifestation of midbrain dysfunction during transtentorial herniation, it is now apparent that this pattern of respiration is more common with unilateral or bilateral hemispheric lesions and is usually a sign of impending coma. This type of breathing may also occur with pontine or medullary lesions. The underlying mechanism of the tachypnea is unknown. It may be the result of either stimulation of receptors in the pulmonary interstitial space secondary to congestion from a neurogenic cause (neurogenic pulmonary edema), or central stimulation of medullary chemoreceptors secondary to local lactate production from tumor or stroke. Rarely, central neurogenic hyperventilation has been reported in anti-NMDA encephalitis.[4]

Other causes of centrally mediated hyperventilation are anxiety, infections, and drugs. The latter either stimulate the central or peripheral chemoreceptors or directly affect the brainstem respiratory neurons.

POSTHYPERVENTILATION APNEA

In normal awake persons, a brief period of apnea follows voluntary hyperventilation. This apnea usually lasts less than 12 seconds and occurs following five deep breaths sufficient to reduce $PaCO_2$ by 8 to 14 mmHg. Apnea lasting more than 12 seconds was found in more than 75 percent of patients with bilateral CNS disease (structural or metabolic), compared to only 1 to 2 percent of normal subjects. It is equally common in patients with unilateral or bilateral brain injury, but is significantly more common in drowsy than alert patients. It is therefore likely that the degree of posthyperventilation apnea is an indicator of depressed CNS function.

APRAXIA OF BREATHING

An inability to take or hold a deep breath in spite of normal motor and sensory functions of bulbar muscles is known as respiratory or breathing apraxia. This abnormality is most often found in elderly patients with cerebrovascular disease, dementia, or lesions of the nondominant hemisphere, and may be associated with frontal lobe release signs, paratonia, or other apraxias.

CLUSTER BREATHING

Cluster breathing is characterized by irregular groups of breaths interspersed with pauses of varying lengths (Fig. 1-2). It may be seen in patients with lower medullary dysfunction or during sleep in patients with MSA.

HICCUP

In hiccup, there is a strong contraction of the diaphragm and intercostal muscles followed by laryngeal closure, usually during inspiration. Hiccup rarely becomes persistent and disabling. A persistent hiccup is associated with lateral medullary lesions, raised intracranial pressure, metabolic encephalopathy from diverse causes such as uremia, and irritation of the diaphragm or phrenic nerves, but in some instances no cause can be found. Uncontrollable hiccups has also been reported in neuromyelitis optica spectrum disorders (NMOSD).

SNEEZING AND YAWNING

These are normal phenomena mediated through respiratory muscles. The center for sneezing is near the nucleus ambiguus, and yawning is coordinated from brainstem sites near the paraventricular nucleus via extrapyramidal pathways. A sneezing reflex triggered by sudden exposure to bright light may be inherited in an autosomal dominant manner. Yawning may initiate temporal lobe seizures, may be associated with arm stretching of the paretic limb in capsular infarction, or occur spontaneously in “locked-in” syndrome.

DIAPHRAGMATIC MYOCLONUS

In diaphragmatic myoclonus or flutter (Leeuwenhoek disease),[5] there is involuntary contraction of the diaphragm during sleep or wakefulness at the rate of approximately 3 Hz. Diaphragmatic contractions cause epigastric pulsations and may be associated with dyspnea, hyperventilation, hiccups, belching, and difficulty in weaning from the ventilator. In the syndrome of isolated diaphragmatic tremor,[6] there is usually no respiratory or functional disability and there is some voluntary control of the phenomenon.

RESPIRATORY DYSFUNCTION FROM NEUROLOGIC DISORDERS

Stroke

The effect of a stroke on respiratory function is highly dependent on the extent and site of the damage.[3] Respiratory compromise in stroke may be due to an infarct or hemorrhage involving structures that regulate breathing or as a consequence of secondary brain edema. In comparison to ischemic strokes, hemorrhagic strokes are more likely to produce early respiratory failure. Neurogenic pulmonary edema is a life-threatening acute respiratory dysfunction that has been reported in a wide range of neurologic conditions such as subarachnoid or intraparenchymal hemorrhage, ischemic stroke, spinal cord and meningeal hemorrhage, head trauma, multiple sclerosis (MS), brain tumor, meningitis and encephalitis, status epilepticus, and acute hydrocephalus. Injury to the brain, specifically the A1 and A5 groups of neurons in the medulla, nucleus of the solitary tract, area postrema, medial reticular nucleus, and dorsal motor nucleus of vagus, has been suggested to produce sympathetic discharges from the hypothalamus, brainstem, and spinal cord that cause severe systemic vasoconstriction and displace blood from the systemic to pulmonary circulation. Concomitantly, there is also reduced left ventricular diastolic and systolic compliance and increased left ventricular volume and left atrial filling pressure. These cardiac changes along with intensive pulmonary vasoconstriction lead to increased pulmonary capillary pressure with endothelial injury and leakage of fluid into the interstitial space and alveoli. This can result in increased pulmonary interstitial and alveolar fluid, leading to pulmonary edema and impaired alveolar gas exchange.

Apnea, hypopnea, ataxic (irregular), tachypneic (central hyperventilation), and periodic (Cheyne–Stokes) breathing patterns have all been reported in stroke, depending on the site of the lesion. Although central neurogenic hyperventilation occurs with midbrain dysfunction from transtentorial herniation, it is also common with unilateral or bilateral hemispheric lesions. Ataxic breathing is more characteristic of medullary lesions and often heralds respiratory failure in patients with large strokes. Breathing abnormalities are common in pontine lesions as well as in secondary brainstem compression from expanding cerebellar hematomas. Infarction of bilateral ventral pons results in the "locked-in" syndrome, where voluntary breathing is paralyzed (and the patient is unable to speak) due to interruption of the corticospinal and corticobulbar pathways. A normally functioning pontine tegmentum, cerebral hemispheres, and medulla results in preserved consciousness and regular automatic ventilation. In contrast, in acquired central hypoventilation syndrome, automatic breathing is disturbed with preserved voluntary breathing. This is usually secondary to bilateral or unilateral medullary infarctions. In focal hemispheric stroke, there may be contralateral dysfunction of chest wall movements.

Apart from anatomic lesions causing respiratory dysfunction, secondary factors following stroke increase the incidence of respiratory failure, such as oropharyngeal hypotonia due to reduced consciousness, impaired swallowing, and aspiration pneumonia.

The need for mechanical ventilation in patients with either brainstem or cerebral hemispheric stroke usually indicates a severe lesion. However, for patients requiring prolonged ventilation and tracheostomy, the likelihood of functional recovery is better in those with brainstem or cerebellar stroke than in those with hemispheric stroke.

Movement Disorders

HYPOKINETIC DISORDERS

Parkinson Disease

Patients with Parkinson disease may have restrictive, obstructive, and mixed types of pulmonary dysfunction, which is more severe in advanced disease and correlates with the degree of rigidity and bradykinesia. The respiratory dysfunction may be categorized as upper airway obstruction, restrictive disorder, a complication of medication intake and withdrawal, and aspiration pneumonia.[5]

Upper airway obstruction is characterized by hypophonia, respiratory flutter, and oro-pharyngeal-laryngeal dystonia. In respiratory flutter, there is regular consecutive flow deceleration and acceleration with a "saw-tooth pattern" on the flow–volume curve resulting from flow oscillation at a frequency of 4 to 8 Hz, which may improve with levodopa. The frequency is similar to that of the limb tremor, and probably results from involuntary movement of intrinsic laryngeal muscles.

The frequency of restrictive respiratory disorders in Parkinson disease ranges from 28 to 85 percent. Rigidity and bradykinesia of the respiratory muscles and loss of chest wall compliance are probably responsible. Respiratory dysfunction can also result from levodopa-induced dyskinesias, which may produce tachypnea, dyspnea, and erratic breathing patterns. Pleuropulmonary fibrosis producing restrictive respiratory dysfunction has been described rarely in patients taking ergot-derived dopamine agonists, such as bromocriptine or pergolide. Acute dopaminergic withdrawal may produce exacerbation of parkinsonism and neuroleptic malignant syndrome. Finally, aspiration pneumonia is the most common cause of death in parkinsonian patients, being implicated in about 70 percent of deaths.

Multiple System Atrophy

Respiratory abnormalities are a major cause of death in MSA, a disorder which often presents with a combination of parkinsonism, autonomic dysfunction, and cerebellar signs. Sleep apneas, both obstructive and central, occur in 15 to 30 percent of patients with MSA.[5] Stridor, including nocturnal stridor, may occur at any stage of the disease and is an important cause of sudden death. Vocal cord dysfunction may result from lower motor neuron weakness of the abducting posterior cricoarytenoid muscles due to degeneration of the nucleus ambiguus or from abnormal overactivity (dystonia) of the adductor muscles due to a defect in central control mechanisms. Other respiratory abnormalities in MSA include central neurogenic hypoventilation resulting in hypercapnic respiratory failure and respiratory dysrhythmias that consist of marked irregularities in tidal and minute volumes, variation of respiratory rate, cluster breathing, apneustic breathing, and periodic breathing.

Perry Syndrome

This is a rare movement disorder characterized by parkinsonism, psychiatric changes, weight loss, and hypoventilation.[7] Respiratory dysfunction is a late feature and the hypoventilation most commonly occurs at night, leading to disrupted sleep. Most patients ultimately die of respiratory failure or pneumonia.

HYPERKINETIC DISORDERS

Tardive Dyskinesia

Respiratory tardive dyskinesia is typically seen in patients already suffering from other symptoms such as oro-lingual-facial stereotypies, body-rocking movements, akathisia, and sensory complaints in addition to tardive dyskinesia.[5] Such patients may present with tachypnea, an irregular respiratory amplitude and rhythm, dyspnea, dysphonia, and vocalizations such as grunting, gasping, and humming.

Dystonia

Severe and acute exacerbations of dystonia are usually observed during a dystonic storm, which is an emergency situation complicated by respiratory failure, muscle breakdown, and myoglobinuria.[5]

Chorea and Huntington Disease

Respiratory dysfunction is frequently observed in the advanced stages of Huntington disease. Patients develop chest wall rigidity, in addition with progressive dysphagia which leads to aspiration pneumonia.[5]

Joubert Syndrome

In Joubert syndrome, episodic hyperventilation and apnea have been reported, probably due to disruption of the cerebellar control pathways for breathing.

Demyelinating Disorders

Respiratory dysfunction contributes significantly to the mortality and morbidity in MS, and respiratory failure is often the cause of death in advanced MS. Demyelinating lesions may involve locations associated with the production or propagation of neural impulses necessary for respiration. The type of dysfunction is dependent on the location and extent of the lesion, and may manifest as either acute or chronic respiratory dysfunction. In MS, the respiratory dysfunction may reflect respiratory muscle weakness, bulbar dysfunction, abnormal control of breathing, sleep-disordered breathing, respiratory failure, or neurogenic pulmonary edema.[8]

Apart from MS, acute respiratory dysfunction has also been reported frequently in other demyelinating disorders such as NMOSD.[9] This group of disorders tends to have a higher frequency of respiratory dysfunction than MS owing to the preferential involvement of the medulla and upper cervical cord.

Neuromuscular Disorders

Neuromuscular disorders (Table 1-1) produce alveolar hypoventilation ($PaCO_2 > 50$ mmHg), hypoxia, and finally apnea in advanced stages. Initially, patients with chronic neuromuscular disorders may not experience dyspnea, as there is decreased exercise demand due to the disease process. Mild respiratory dysfunction may present with signs of anxiety, sweating, tachycardia, and tachypnea, accompanied by a reduced single-breath count, decreased chest expansion, paradoxical inward movement of the abdomen during inspiration (suggesting diaphragmatic weakness), interrupted speech, and poor cough.[10]

TABLE 1-1 ■ Common Neuromuscular Disorders Causing Respiratory Failure

Anterior horn cell disorders
Motor neuron disease
Spinal muscular atrophy
Poliomyelitis
Neuropathies
Guillain–Barré syndrome
Phrenic neuropathy
Critical illness polyneuropathy
Hereditary neuropathy
Multifocal motor neuropathy with conduction block
Neuromuscular junction disorders
Myasthenia gravis and congenital myasthenic syndrome
Lambert–Eaton myasthenic syndrome
Toxins and drugs
Myopathies
Muscular dystrophies
Congenital myopathies
Critical illness myopathy

ANTERIOR HORN CELL DISORDERS

Amyotrophic Lateral Sclerosis

Respiratory failure, which usually occurs late in the disease, is the most important cause of death in amyotrophic lateral sclerosis (ALS). The pathogenesis of respiratory failure is multifactorial and includes diaphragmatic weakness from loss of anterior horn cells in the cervical spinal cord, weakness of the chest wall from loss of thoracic spinal motor neurons, bulbar disease, and loss of descending corticospinal projections to the cervical and thoracic anterior horn cells.[10]

Pulmonary function tests (especially the FVC) are useful in monitoring the course of respiratory failure in the disease. Bilevel intermittent positive pressure ventilation improves survival and slows decline of pulmonary function, especially in bulbar-onset forms. This treatment should be offered to patients at the onset of dyspnea, when FVC falls below 50 percent of normal, or when there is a rapid decline in FVC. Rarely, some patients present initially with acute respiratory failure.

The duration of symptoms such as exertional dyspnea or orthopnea varies from weeks to months. Once mechanical ventilation is needed due to hypercapnia, successful weaning is unlikely. Planning in advance for respiratory failure in the terminal stages of ALS is important, and patients' wishes regarding prolonged ventilation and intubation should be discussed.

Other Anterior Horn Cell Disorders

Acute poliomyelitis is now a rare cause of respiratory failure in children, which occurs due to involvement of the anterior horn cells of the spinal cord and brainstem. Occasionally, in survivors of acute poliomyelitis, respiratory weakness may reappear after several years along with limb weakness, especially in those who had the illness after 10 years of age and those who presented initially with respiratory failure.[10] Other viral infections, including West Nile virus encephalomyelitis, are now more common causes of a poliomyelitis-like illness worldwide.

Respiratory insufficiency also occurs in spinal muscular atrophy (SMA), specifically in type 1 (Werdnig-Hoffman disease). It may occur to a variable extent in SMA type 2, and is uncommon in type 3.[10]

NEUROPATHIES

Guillain–Barré Syndrome

Acute inflammatory demyelinating polyneuropathy, of which Guillain–Barré syndrome is the prototype, is one of the most important and common neurologic causes of respiratory dysfunction. The main cause of respiratory failure in these conditions is phrenic nerve demyelination and consequent diaphragmatic paralysis.[10] Other contributory factors include weakness of the intercostal and other accessory muscles of respiration, autonomic dysfunction, retained respiratory secretions, and atelectasis. Approximately one-third of patients are ready for weaning within 2 weeks, but those with axonal forms have a poorer prognosis for respiratory recovery and may therefore require earlier tracheostomy. Immune therapy probably reduces the length of ventilator dependence.

Early respiratory symptoms of discomfort and agitation are accompanied by signs of reduced single-breath count, weak cough, use of accessory muscles, tachypnea, paradoxical abdominal movement, and speech interrupted by brief breaths. There may be frequent awakenings at night resulting from relaxation of voluntarily activated respiratory muscles during REM sleep, which increases demand on an already weakened diaphragm.

Indications for mechanical ventilation include a vital capacity less than 20 mL/kg, maximum inspiratory pressure below 25 cmH_2O, and a maximum expiratory pressure less than 40 cmH_2O. Mechanical ventilation will probably be required within 36 hours if the FVC is less than 50 percent of baseline. Even patients with a normal vital capacity may be at risk of imminent respiratory failure when the phrenic nerves are involved by the demyelinating process. Abnormal phrenic nerve conduction studies and needle electromyography of the diaphragm may predict respiratory insufficiency.

Phrenic Neuropathies

The severity of symptoms in phrenic neuropathies is variable and depends on the underlying cause, such as trauma, tumor infiltration, compression, infection, radiation, or an idiopathic process. Symptoms include exertional shortness of breath, and the respiratory rate may increase when lying flat. In addition to an elevated hemidiaphragm on chest radiography, there may be pulmonary atelectasis on the paralyzed side and mediastinal shift toward the normal side. Clinically, uninhibited movement of the costal margin away from the midline on the side of injury may be observed during inspiration. On fluoroscopy, the affected diaphragm moves paradoxically upward with a vigorous sniff (Kienback sign). Phrenic nerve conduction studies and needle electromyography of the diaphragm are useful for diagnosis and prognosis.

Critical Illness Polyneuropathy

In an intensive care unit, unexplained difficulty in weaning from the ventilator may result from several neuromuscular conditions that may occur in patients with the systemic inflammatory response syndrome. This syndrome occurs in 20 to 50 percent of patients in major medical or surgical care units, and its associated damage to the peripheral nervous system is probably related to the release of inflammatory mediators such as cytokines and free radicals.[10]

Critical illness polyneuropathy is a predominantly motor, axonal polyneuropathy that occurs in 50 to 70 percent of patients with systemic inflammatory response syndrome. The initial manifestation is often difficulty in weaning from the ventilator, despite systemic improvement. Weakness is usually equally distributed in both proximal and distal muscle groups. Severe weakness with muscle wasting is observed in one-third of patients, diminished or absent muscle stretch reflexes in the majority, and distal sensory loss in less than one-third. Electrophysiologic studies show reduced amplitude of compound muscle action potentials as early as 2 weeks from the onset of the systemic inflammatory response syndrome, with abnormal spontaneous activity seen in muscles; sensory nerve action potentials may be normal. Phrenic nerve stimulation and diaphragmatic electromyography are sometimes helpful in critical illness polyneuropathy, and degeneration of the phrenic nerves and denervation atrophy of respiratory muscles may be found at autopsy.

Other Neuropathies

Respiratory failure resulting from phrenic nerve involvement has been reported in other acquired and inherited neuropathies such as those of diabetes mellitus, chronic renal failure, sarcoidosis, leprosy, diphtheria, multifocal motor neuropathy with conduction block, infantile axonal polyneuropathy, hereditary motor and sensory neuropathy type 2C, arsenic exposure, lead toxicity, and acute organophosphate poisoning.[10]

NEUROMUSCULAR JUNCTION DISORDERS

Neuromuscular junction disorders should be suspected in patients with respiratory muscle weakness of unclear origin. These disorders may occur at any age, and the underlying causes include autoimmune, hereditary, paraneoplastic, and toxic diseases.[10]

Progressive respiratory muscle weakness is commonly found in generalized myasthenia gravis. During the course of the illness, 15 to 20 percent of patients will develop a myasthenic crisis, characterized by acute respiratory failure requiring mechanical ventilation, with a mortality rate of up to 5 percent. Infections are the most common trigger for myasthenic crisis; other precipitants include initial corticosteroid therapy, neuromuscular blocking drugs such as aminoglycosides, surgery, pregnancy and delivery, and physical and emotional stresses.

Although myasthenic crisis occurs most often in generalized myasthenia gravis, it may also occur rarely in oculobulbar variants, and isolated respiratory failure may be the initial manifestation of myasthenia gravis. Antibodies against acetylcholine receptors may not be present in patients with predominant respiratory muscle involvement. Instead, some of these patients may have muscle-specific tyrosine kinase receptor antibodies and have predominantly neck, shoulder, and respiratory muscle or oculobulbar weakness.

Excessive administration of anticholinesterase drugs to treat myasthenia gravis may sometimes leads to respiratory weakness. Meiosis, sweating, abdominal cramping and diarrhea, excessive secretions, and muscle fasciculations characterize these cholinergic crises. Bronchospasm, aspiration, and excessive inspissated secretions with weak cough cause the respiratory dysfunction.

In addition to serum antibody tests, the evaluation of patients with respiratory insufficiency and suspected myasthenia gravis may include repetitive nerve stimulation studies, occasionally including the phrenic nerve, and single-fiber electromyography if the diagnosis remains unclear. The edrophonium

(Tensilon) test may not change respiratory muscle strength and is most useful when the patient has ptosis. Phrenic nerve conduction studies may be useful to exclude iatrogenic phrenic nerve injury in post-thymectomy myasthenia gravis patients with respiratory insufficiency.

Other neuromuscular junction disorders that may cause respiratory insufficiency include other forms of myasthenic gravis (neonatal, congenital, and juvenile). Isolated or predominant involvement of the respiratory muscles is not uncommon and may be the presenting feature of Lambert–Eaton myasthenic syndrome. In addition, acquired causes include foodborne or wound botulism, and neuromuscular toxins and drugs.

MYOPATHIES

Muscular Dystrophies

Among the dystrophinopathies, Duchenne muscular dystrophy is the most common cause of respiratory muscle weakness; approximately 40 to 70 percent of these patients die of respiratory failure. Respiratory insufficiency starts at the age of 8 or 9 years and progressively increases with age and functional disability. Those with more severe thoracic scoliosis have earlier onset of respiratory failure. The causes of respiratory failure include weakness of inspiratory and expiratory muscles, progressive kyphoscoliosis, recurrent respiratory tract infections, and pulmonary edema from cardiac failure.[10] Respiratory insufficiency is less frequent in Becker muscular dystrophy. Early respiratory insufficiency and death in infancy may also occur in isolated muscular dystrophy involving the diaphragm.

Respiratory involvement is common in myotonic dystrophy and results from weakness of the diaphragm and the intercostal muscles. The cause of respiratory muscle weakness is due to CNS involvement in 20 percent of patients. Other contributory factors include the concurrence of various types of neuropathy. Alveolar hypoventilation from diaphragmatic weakness and central hypoventilation (from neuronal loss in the dorsal raphe and superior central nuclei) underlie the hypersomnia that is common in myotonic dystrophy.

Respiratory muscle weakness has also been frequently reported in limb-girdle muscular dystrophy, specifically types 2C, 2D, 2E, and 2F, which are sarcoglycanopathies.[10]

Critical Illness Myopathy

Critically ill patients may be affected by a critical illness myopathy in addition to the neuropathy discussed earlier.[10] This includes at least three different types of muscle abnormalities: thick filament myopathy, acute necrotizing myopathy, and cachectic myopathy. Flaccid weakness of the muscles of all limbs, neck flexors, and sometimes the face is accompanied by diaphragmatic weakness and difficulty in weaning from mechanical ventilation. Differentiation of critical illness myopathy from neuropathy may be difficult and some patients, if not most, will have a combination of these two entities. Myopathic features on electrophysiologic studies, an elevated serum creatine kinase level (which is not always present), and demonstration of myopathic features with myosin loss on histopathology are supportive of critical illness myopathy.

Other Muscle Disorders

Many patients with various limb-girdle syndromes have dyspnea on exertion, chronic cough, and recurrent respiratory infections. Those with severe diaphragmatic involvement may have chronic alveolar hypoventilation resulting in morning headaches, excessive sleepiness, fatigue, and altered mentation. Although patients with facioscapulohumeral and scapuloperoneal syndromes are usually spared respiratory muscle involvement, they may develop frequent aspiration pneumonia due to weakness of pharyngeal muscles.[10]

Congenital myopathies are usually nonprogressive or slowly progressive muscle diseases that are present at birth, but in severe cases respiratory insufficiency can occur. Respiratory muscle weakness has been reported in infants with nemaline myopathy, centronuclear myopathy, and multicore myopathy.[10]

In inflammatory myopathies (e.g., polymyositis and dermatomyositis), pulmonary complications are frequently the result of weakness of respiratory muscles, interstitial lung disease, and aspiration pneumonia from weakness of pharyngeal and upper esophageal muscles.

Respiratory insufficiency is a critical component of acid maltase deficiency (Pompe disease). In the infantile form, death usually occurs before age 2 due to respiratory insufficiency. Proximal limb or respiratory muscle weakness is the presenting features in the childhood form. In the adult form, involvement of the respiratory muscles is common and patients may present with an acute-on-chronic respiratory failure.[10] Respiratory muscle weakness has also been reported in corticosteroid-induced myopathy as a result of selective atrophy of type IIB fibers, in HIV myopathy, mitochondrial myopathies, and carnitine palmitoyl transferase deficiency.

Spinal Cord Lesions

Similar to stroke, the effect of a spinal cord lesion on breathing is highly dependent on the level of the lesion.[3] Most often, respiratory dysfunction is reported secondary to trauma. However, similar abnormalities may also be reported in vascular or neoplastic conditions.

CERVICAL SPINAL CORD INJURY

Injury to the upper cervical spinal cord above the phrenic nerve outflow, that is, at C1 or C2, results in paralysis of all the key respiratory muscles due to interruption of descending pathways.[3] In such situations, apnea is rapidly followed by death unless ventilator support is provided. Lower lesions in the cervical cord spinal produce loss of intercostal and expiratory action, with normal diaphragmatic and inspiratory accessory musculature. Delayed apnea in patients with cervical injury may arise secondary to manipulation of the spine in order to stabilize a fracture. In chronic injury, spasticity of the respiratory muscles may compromise vital capacity and inspiratory pressure. Dyspnea and wheezing in patients with spinal cord injury can also result from vagal overactivity due to sympathetic denervation.

THORACIC CORD INJURY

Lesions of the thoracic spinal cord seldom produce significant respiratory abnormalities, and the most important consequence of such an injury is reduced force of coughing due to paralysis or weakness of abdominal muscles.[3]

Miscellaneous Disorders

EPILEPSY

Sudden unexpected death in epilepsy is a major cause of epilepsy-related mortality. A higher prevalence has been reported in patients with generalized tonic-clonic seizures and refractory epilepsy. An epilepsy-related cardiorespiratory autonomic dysfunction has been implicated in its pathogenesis.

BRAIN TUMORS

Brainstem tumors such as gliomas, ependymomas, medulloblastomas, and cerebellar astrocytomas are more likely to cause acute respiratory disturbances than tumors in the cerebral hemispheres. Postoperative ventilatory support is often required. Supratentorial gliomas and other masses may also affect respiration due to tentorial herniation.

DISORDERS OF BREATHING ASSOCIATED WITH SLEEP

Upper Airway Obstruction

Upper airway obstruction during sleep is defined as partial (obstructive sleep hypopnea) or complete (obstructive sleep apnea) obstruction to airflow proximal to the larynx for at least 10 seconds despite ongoing respiratory efforts. There may be a mixed apnea (initial lack of respiratory effort followed by increasing effort) and upper airway resistance syndrome (frequent respiratory effort-related arousals).[1] These conditions are collectively referred to as obstructive sleep apnea/hypopnea syndrome (OSAHS).

Stridor, a harsh or strained, high-pitched inspiratory sound, results from obstruction to inspiration at the level of the vocal cords. Several neurologic causes may result in stridor including brainstem dysfunction (e.g., from Chiari malformation), paralysis of cord abduction from recurrent laryngeal neuropathy, dystonia of the vocal-cord adductor muscles, and MSA.

Both OSAHS and stridor have been observed in anti-IgLON5 disease,[11] a recently described disorder characterized by NREM and REM parasomnias, in addition to OSA and stridor. Symptoms are progressive and can lead to life-threatening respiratory dysfunction such as central hypoventilation.

Central Sleep Apnea Syndromes

CSA syndromes are characterized by disordered breathing during sleep associated with reduced or absent respiratory effort, in addition to excessive daytime sleepiness, frequent nocturnal awakenings, or both. Six types have been identified: primary CSA; CSA due to Cheyne–Stokes breathing; CSA due to medical condition not Cheyne–Stokes; CSA due to high-altitude periodic breathing; CSA due to drugs or substances; and primary sleep apnea of infancy.[12]

CSA may be associated with hypercapnia or normocapnia/hypocapnia. In hypercapnic CSA, the ventilatory response to CO_2 is reduced. The disorder occurs in patients with alveolar hypoventilation caused by neuromuscular disorders, brainstem dysfunction, or in idiopathic alveolar hypoventilation syndrome. Normocapnic or hypocapnic CSA may also be idiopathic or it may occur in the setting of high altitude, with Cheyne–Stokes respiration, or with partial upper airway obstruction.

CSA is less common than OSAHS. Esophageal pressure monitoring is the definitive technique used to differentiate central from peripheral obstructive events. However, the differentiation can usually be made by documentation of cessation of airflow associated with absence of respiratory effort.

Sleep Hypoventilation Syndrome

Sleep hypoventilation syndrome is characterized by both hypercapnia and hypoxemia during sleep, unexplained by discrete apneas or hypopneas. A variety of neurologic disorders may cause this disorder (Table 1-2) by affecting the central respiratory centers or their efferent pathways, or by myopathies or neuropathies affecting the diaphragm or intercostal muscles. Sleep hypoventilation syndrome is initially observed in REM sleep, but eventually daytime respiratory failure occurs. Sleep hypoventilation syndrome results in frequent nocturnal arousals, nocturnal dyspnea on lying flat, morning headaches, and daytime sleepiness. Chronic hypercapnia may result in blunting of respiratory chemoreceptor responses and a secondary reduction in central respiratory drive. Nocturnal hypoventilation results in erythrocytosis, pulmonary hypertension, and, in severe cases, cor pulmonale.

TABLE 1-2 ■ Neurologic Causes of Sleep Hypoventilation Syndrome

Disorders of brainstem respiratory centers
Idiopathic central alveolar hypoventilation
Multiple system atrophy
Infarcts or hemorrhage
Tumors
Infections (e.g., encephalitis)
Arnold–Chiari malformation
Disorders of spinal efferent pathways
High spinal cord trauma
Cervical posterior cordotomy
Multiple sclerosis
Disorders of anterior horn cells and peripheral nerves
Poliomyelitis and postpolio syndrome
Motor neuron diseases
Generalized peripheral neuropathies
Bilateral phrenic neuropathy
Disorders of muscle
Congenital myopathies
Muscular dystrophies
Inflammatory myopathies
Myasthenia gravis
Disorders restricting chest cage movement
Kyphosis
Scoliosis in chronic neurodegenerative disorders

Adapted with permission from Bolton CF, Chen R, Wijdicks EFM, et al: Neurology of Breathing. Butterworth Heinemann, Philadelphia, 2004.

Respiratory Dysrhythmias

Respiratory dysrhythmias are abnormalities of the rhythm of breathing or the relationship of inspiration to expiration. They occur more frequently during sleep and include Cheyne–Stokes breathing, apneustic breathing, irregular or ataxic breathing, and cluster breathing. The clinical features of these abnormal patterns of respiration were discussed earlier. Cheyne–Stokes breathing may be associated with CSA and is often observed in patients with cardiac failure.

Sudden Infant Death Syndrome

Prolonged laryngeal chemoreflex, blunted chemo- and arousal reflexes, autonomic dysregulation, sleep apnea, and genetic polymorphisms have been implicated in the pathogenesis of sudden infant death syndrome.[1]

NEUROLOGIC EFFECTS OF RESPIRATORY DYSFUNCTION

Like other organs in the body, the brain is often affected indirectly by respiratory failure. Neurologic symptoms may be acute or insidious, and signs of primary lung disease may not always be apparent.

Dysfunction Related to Pulmonary Pathology

Chronic or acute hypoxia and hypercapnia, or hypocapnia, can result from diverse primary lung disorders or cardiac illness. These abnormalities can impair the function of the nervous system in several ways.[13]

HYPOXIA

Cerebral dysfunction usually occurs with reduction of partial pressure of oxygen to less than 40 mmHg. The effects of pure hypoxia on the brain (hypoxic hypoxia) are observed in high-altitude sickness. Several days after ascending rapidly (usually to altitudes of 8,000 to 12,000 ft), headache, insomnia, anorexia, nausea, vomiting, and impaired cognitive function may occur. In the more acute and severe form (usually above 10,000 ft), there is severe headache, delirium, hallucinations, ataxia, and occasionally seizures. Papilledema and retinal hemorrhages may occur, probably due to cerebral edema. Prophylactic acetazolamide and dexamethasone are sometimes useful, and dexamethasone is used to treat the disorder when it occurs.

Following cardiac arrest, patients can develop an encephalopathy, primarily as a result of cerebral ischemia rather than pure hypoxia. Structural abnormalities usually do not occur in the brain in the setting of hypoxia without ischemia. Several movement disorders such as dystonia, chorea, myoclonus, tremor, and akinetic-rigid syndromes also have been known to arise as a consequence of hypoxia.

HYPERCAPNIA

Chronic pulmonary insufficiency is one of the important causes of chronic hypercapnia ($PaCO_2$ levels ranging from 39 to 68 mmHg). Headache, papilledema, tremulousness, asterixis, altered consciousness, and generalized slowing of the electroencephalogram may be observed secondary to the hypercapnia. Raised intracranial pressure from chronic CO_2 narcosis is believed to be the underlying factor causing headache and papilledema. Management strategies include discontinuation of sedative drugs, avoidance of vigorous hyperventilation, and ventilatory support. Cognitive impairment in the domains of attention, memory, learning, executive skills, language, visuospatial and constructional abilities, and psychomotor speed have been reported in patients with chronic obstructive pulmonary disease. Chronic hypercapnia, hypoxemia, and hypoventilation are implicated in the above impairment.[14]

Encephalopathy and occasionally seizures are the main symptoms of acute severe hypercapnia with CO_2 levels ranging from 75 to 110 mmHg. CO_2 narcosis results in reduced pH of the CSF and subsequent respiratory acidosis. Acute encephalopathy probably results from hydrogen ion-induced inhibition of glutamate receptors.

Dysfunction Related to Obstructive Sleep Apnea

OSA is the most common sleep-related breathing disorder and several studies have reported the impact of OSA on neurocognitive functions, and neurologic deficits, specifically neurodegeneration, epilepsy, stroke, and headache.[15]

VASCULAR DISORDERS

OSA-related hypoxemia has been reported to change the structure and function of blood vessels. Furthermore, snoring is a risk factor for stroke, and a higher frequency of OSAHS has been observed in patients who had suffered a stroke. Hypertension, cardiac arrhythmias, increased platelet aggregation, increased blood viscosity, decreased fibrinolysis, sympathetic hyperactivity, and changes in cerebral blood flow are each a potential mechanism for stroke in patients with OSAHS.

COGNITIVE DYSFUNCTION

Patients with OSA have been reported to demonstrate cognitive impairment in the domains of concept formation, executive functioning, attention, speed of processing, working and verbal memory, nonverbal memory, psychomotor speed, motor control and performance, construction, verbal functioning and verbal reasoning, and perception. These abnormalities have been attributed to sleep fragmentation and hypoxemia, which can produce structural brain damage and excessive daytime sleepiness. Continuous positive airway pressure has been found to be moderately effective in reducing the neurocognitive deficits in patients with OSA and excessive daytime sleepiness.

HEADACHE

Early morning headache and cluster headache have been associated with OSAHS, and treatment with positive airway pressure improves headache in these patients. Hypoxia or hypercapnia-induced cerebral vasodilation is the most likely mechanism of the headache. Although the exact frequency of headache in OSAHS is not known, it is more frequent in OSA and snorers than those without these disorders.

EPILEPSY

Several studies have investigated the relationship and prevalence of OSA in patients with epilepsy. OSA may be implicated as a trigger for seizures by producing sleep disruption, sleep deprivation, and cerebral hypoxemia.

CONCLUDING COMMENTS

Respiration involves a complex interplay between the nervous and respiratory systems. The nervous system plays a critical role in the maintenance of this predominantly involuntary function via anatomic and functional pathways that span the neuraxis. Damage to either the central or peripheral components of these pathways can adversely affect respiration. Conversely, hypoxia and hypercapnia secondary to respiratory dysfunction may also produce neurologic complications. A thorough understanding of respiratory physiology, detailed clinical examination, and judicial use of investigations are crucial for appropriate management of patients.

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CHAPTER

2

Neurologic Complications of Aortic Disease and Surgery

DOUGLAS S. GOODIN

CLINICAL NEUROLOGIC SYNDROMES DUE TO AORTIC PATHOLOGY
- Spinal Cord Ischemia
  - *Anatomy*
  - *Ischemic Cord Syndromes*
- Cerebral Ischemia
  - *Anatomy*
  - *Strokes and Transient Ischemic Attacks*
- Peripheral Neuropathy
  - *Mononeuropathies*
  - *Radiculopathies*
  - *Polyneuropathies*
  - *Autonomic Neuropathies*

AORTIC DISEASES AND SURGERY
- Aortitis
  - *Syphilitic Aortitis*
  - *Takayasu Arteritis*
  - *Giant Cell Arteritis*
- Aortic Aneurysms
  - *Nondissecting Aneurysms*
  - *Dissecting Aortic Aneurysms*
  - *Traumatic Aortic Injury*
- Coarctation of the Aorta
- Surgery and Other Procedures
  - *Aortic Surgery*
  - *Aortography and Other Procedures on the Aorta*
  - *Intraoperative Adjuncts to Avoid Spinal Cord Ischemia*

The aorta is the main conduit through which the heart supplies blood to the body, including the brain, brainstem, and spinal cord. In addition, this vessel is situated close to important neural structures. In consequence, both disease of the aorta and operations on it may have profound but variable effects on nervous system function. Often the neurologic syndrome produced by aortic disease or surgery depends more on the part of the aorta involved than on the nature of the pathologic process itself. For example, either syphilis or atherosclerosis may produce symptoms of cerebral ischemia if the disease affects the aortic arch or of spinal cord ischemia if the pathologic process is in the descending thoracic aorta. Even when the nature of the pathologic process is important in determining the resultant neurologic syndrome, several diseases may result in the same pathologic process. Thus, atherosclerosis, infection, inflammation, and trauma may each result in the formation of aortic aneurysms; similarly, coarctation of the aorta may be congenital, a result of Takayasu arteritis, or a sequela of radiation exposure during childhood.

The initial focus of this chapter is on the three major areas of neurologic dysfunction resulting from aortic disease and surgery: spinal cord ischemia, cerebral ischemia, and peripheral neuropathy. Specific conditions that merit special consideration are then discussed individually. The normal anatomic relationships are also considered in order to provide insight into the pathogenesis of the resulting neurologic syndromes.

CLINICAL NEUROLOGIC SYNDROMES DUE TO AORTIC PATHOLOGY

Aortic disease may produce a variety of neurologic syndromes. The specific syndrome depends to a large extent on the site of involvement along the aorta.

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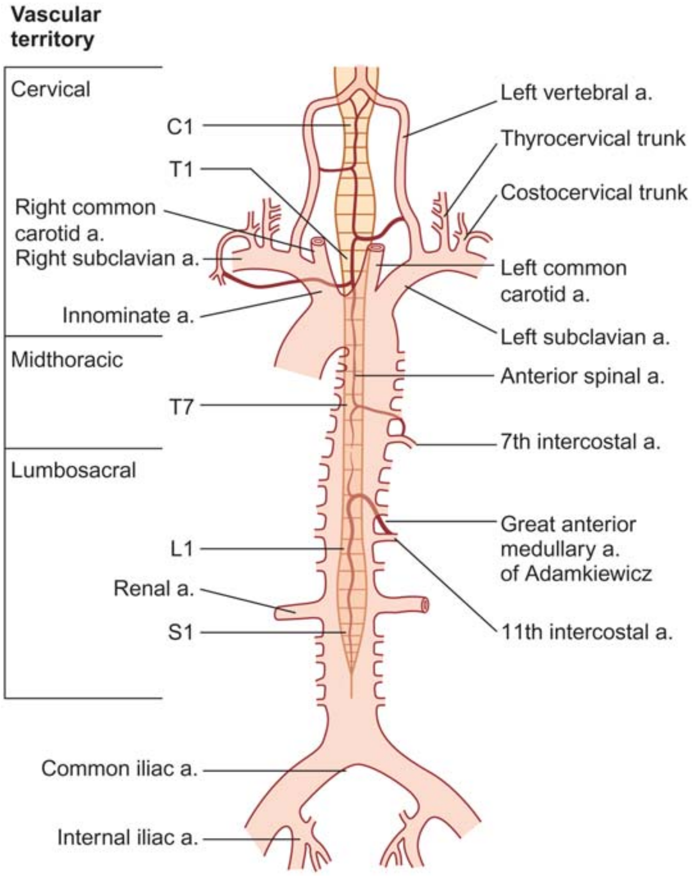
Vascular territory
Cervical
C1
T1
Right common carotid a.
Right subclavian a.
Innominate a.
Midthoracic
T7
Lumbosacral
L1
Renal a.
S1
Common iliac a.
Internal iliac a.
Left vertebral a.
Thyrocervical trunk
Costocervical trunk
Left common carotid a.
Left subclavian a.
Anterior spinal a.
7th intercostal a.
Great anterior medullary a. of Adamkiewicz
11th intercostal a.

FIGURE 2-1 ■ Extraspinal contributions to the anterior spinal arteries showing the three arterial territories. In the cervical region, an average of three arteries (derived from the vertebral arteries and the costocervical trunk) supply the anterior spinal artery. The anterior spinal artery is narrowest in the midthoracic region, often being difficult to distinguish from other small arteries on the anterior surface of the cord; occasionally it is discontinuous with the anterior spinal artery above and below. In addition, this region is often supplied by only a single small radiculomedullary vessel. The lumbosacral territory is supplied by a single large artery, the great anterior medullary artery of Adamkiewicz, which turns abruptly caudal after joining the anterior spinal artery. If it gives off an ascending branch, that branch is usually a much smaller vessel. This artery is usually the most caudal of the anterior radiculomedullary arteries, but when it follows a relatively high thoracic root, there is often a small lumbar radiculomedullary artery below. In this and subsequent illustrations, *a* indicates artery; *m*, muscle; *n*, nerve.

Spinal Cord Ischemia

ANATOMY

Embryologic Development

During embryologic development, primitive blood vessels arise along the spinal nerve roots bilaterally and at each segmental level. Each of these segmental vessels then divides into anterior and posterior branches, which ramify extensively on the surfaces of the developing spinal cord. As development proceeds, most of these vessels regress and a few enlarge, so that by birth, the blood supply to the spinal cord depends on a small but highly variable number of persisting segmental vessels (Fig. 2-1). In the thoracic region, where the aorta is situated to the left of the midline, the persisting vessels entering the spinal canal are those from the left in 70 to 80 percent of cases.

Anterior Spinal Artery

The anterior spinal artery is formed rostrally from paired branches of the intracranial vertebral arteries that descend from the level of the medulla (Fig. 2-1). These two arteries fuse to form a single anterior spinal artery that overlies the anterior longitudinal fissure of the spinal cord. This artery is joined at different levels by anterior radiculomedullary arteries,

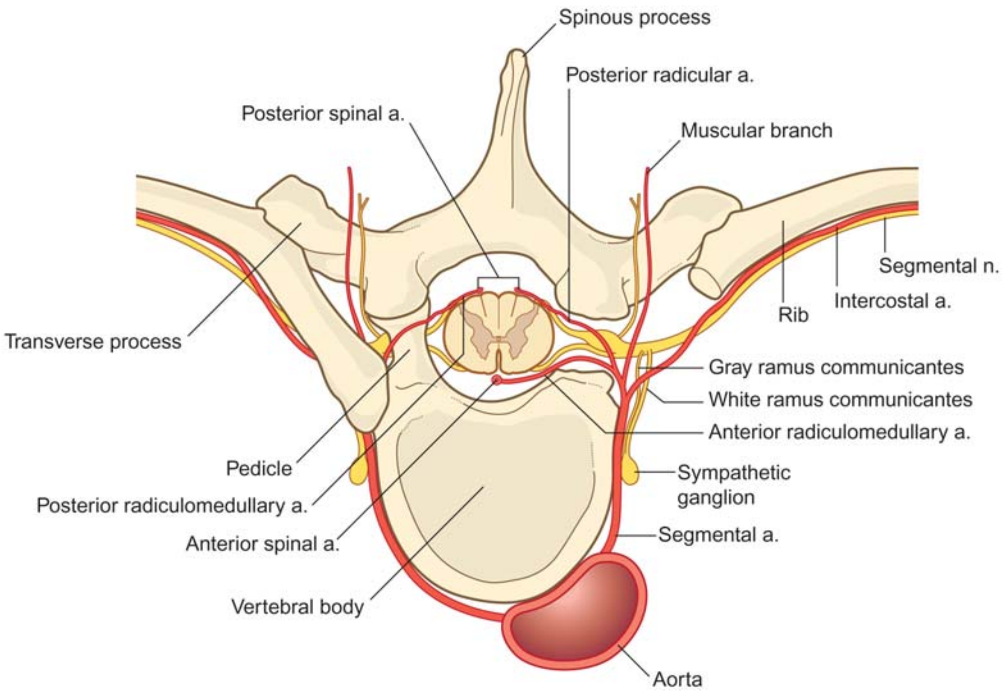
Spinous process
Posterior radicular a.
Posterior spinal a.
Muscular branch
Segmental n.
Intercostal a.
Rib
Transverse process
Gray ramus communicantes
White ramus communicantes
Anterior radiculomedullary a.
Pedicle
Sympathetic ganglion
Posterior radiculomedullary a.
Segmental a.
Anterior spinal a.
Vertebral body
Aorta

FIGURE 2-2 ■ Anatomy of the spinal cord circulation, showing the relationship of the segmental arteries and their branches to the spinal canal and cord. The left rib and the left pedicle of the vertebra have been cut away to show the underlying vascular and neural structures.

which are branches of certain segmental vessels (Fig. 2-2). The number of these vessels is variable among individuals, ranging from 2 to 17, although 85 percent of individuals have between 4 and 7.

The anterior spinal artery in the region that includes the cervical enlargement (C1 to T3) is particularly well supplied, receiving contributions from an average of three segmental vessels. One constant artery arises from the costocervical trunk and supplies the lower segments; the others arise from the extracranial vertebral arteries and supply the middle cervical segments. In addition, branches of the vertebral arteries have rich anastomotic connections with other neck vessels, including the occipital artery, deep cervical artery, and ascending cervical artery.

The anterior spinal artery in the midthoracic portion of the cord (T4 to T8) often receives only a single contribution from a small artery located at about T7, most often on the left. The anterior spinal artery has its smallest diameter in this region, and it is sometimes—but not usually—discontinuous with the vessel in more rostral or caudal regions.

The anterior spinal artery in the region of the lumbar enlargement (T9 to the conus medullaris) is, as at the cervical enlargement, richly supplied, deriving its blood supply predominantly from a single large (1.0 to 1.3 mm in diameter) artery, the great anterior medullary artery of Adamkiewicz. This artery almost always accompanies a nerve root between T9 and L2, usually on the left, although rarely it may accompany a root above or below these levels. Identification of the actual location of this great vessel has become an important part of the planning and execution of operations on the aorta such as repair of thoracoabdominal aortic aneurysms. Although digital subtraction angiography has been used for this purpose, the use of contrast-enhanced magnetic resonance angiography is a noninvasive alternative. Caudally, at the conus medullaris, the anterior spinal artery anastomoses with both posterior spinal arteries.

Posterior Spinal Arteries

The paired posterior spinal arteries form rostrally from the intracranial portion of the vertebral arteries. They are distinct paired vessels only at their origin, however, and thereafter become intermixed with an anastomotic posterior pial arterial plexus (Fig. 2-3). This plexus is joined at different levels by a variable number (10 to 23) of posterior

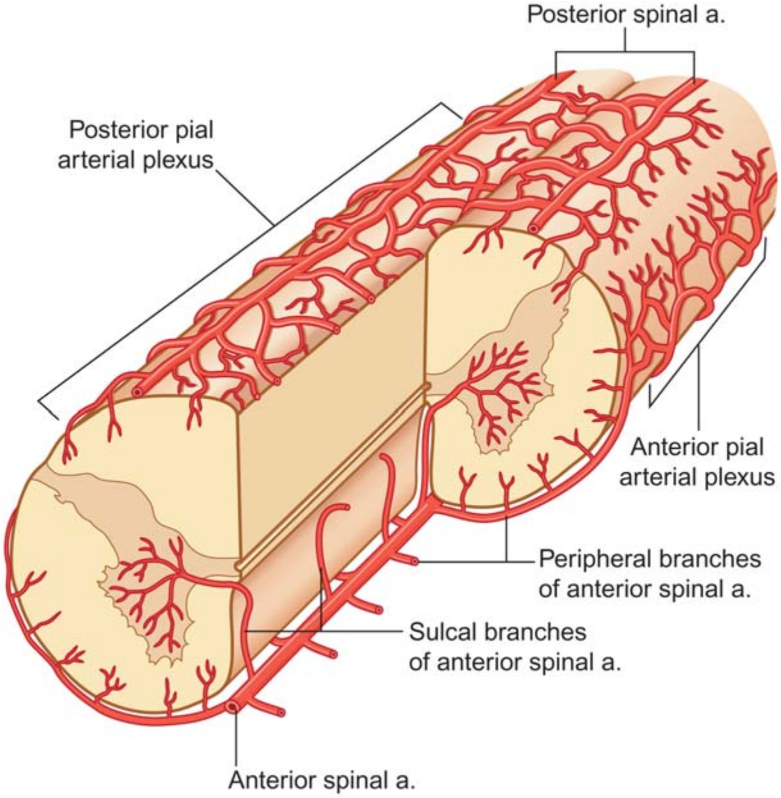
Posterior spinal a.
Posterior pial arterial plexus
Anterior pial arterial plexus
Peripheral branches of anterior spinal a.
Sulcal branches of anterior spinal a.
Anterior spinal a.

FIGURE 2-3 ■ Vascular anatomy of the spinal cord. The anterior spinal artery gives off both peripheral and sulcal branches. The sulcal branches pass posteriorly, penetrating the anterior longitudinal fissure. On reaching the anterior white commissure, they turn alternately to the right and to the left to supply the gray matter and deep white matter on each side. Occasionally two adjacent vessels pass to the same side, and on other occasions, a common stem vessel bifurcates to supply both sides. Terminal branches of these vessels overlap those from vessels above and below on the same side of the cord. The peripheral branches of the anterior spinal artery pass radially and form an anastomotic network of vessels, the anterior pial arterial plexus, which supplies the anterior and lateral white matter tracts by penetrating branches. The posterior pial arterial plexus is formed as a rich anastomotic network from the paired posterior spinal arteries. Penetrating branches from this plexus supply the posterior horns and posterior funiculi.

radiculomedullary vessels that accompany the posterior nerve roots.

Intrinsic Blood Supply of the Spinal Cord

In contrast to the extreme interindividual variability in the extraspinal arteries that supply the spinal cord, the intrinsic blood supply of the cord itself is more consistent. The anterior spinal artery gives off central (sulcal) arteries that pass posteriorly, penetrating the anterior longitudinal fissure and supplying most of the central gray matter and the deep portion of the anterior white matter (Fig. 2-4). The number of these sulcal vessels is variable, with 5 to 8 vessels per centimeter in the cervical region, 2 to 6 vessels per centimeter in the thoracic region, and 5 to 12 vessels per centimeter in the lumbosacral region.

The anterior spinal artery also gives off peripheral arteries that pass radially on the anterior surface of the spinal cord to supply the white matter tracts anteriorly and laterally. These arteries form the anterior pial arterial plexus, which is often poorly anastomotic with its posterior counterpart. The posterior horns and posterior funiculi are supplied by penetrating vessels from the posterior pial arterial plexus.

ISCHEMIC CORD SYNDROMES

Ischemia of the spinal cord may be produced either by the interruption of blood flow through

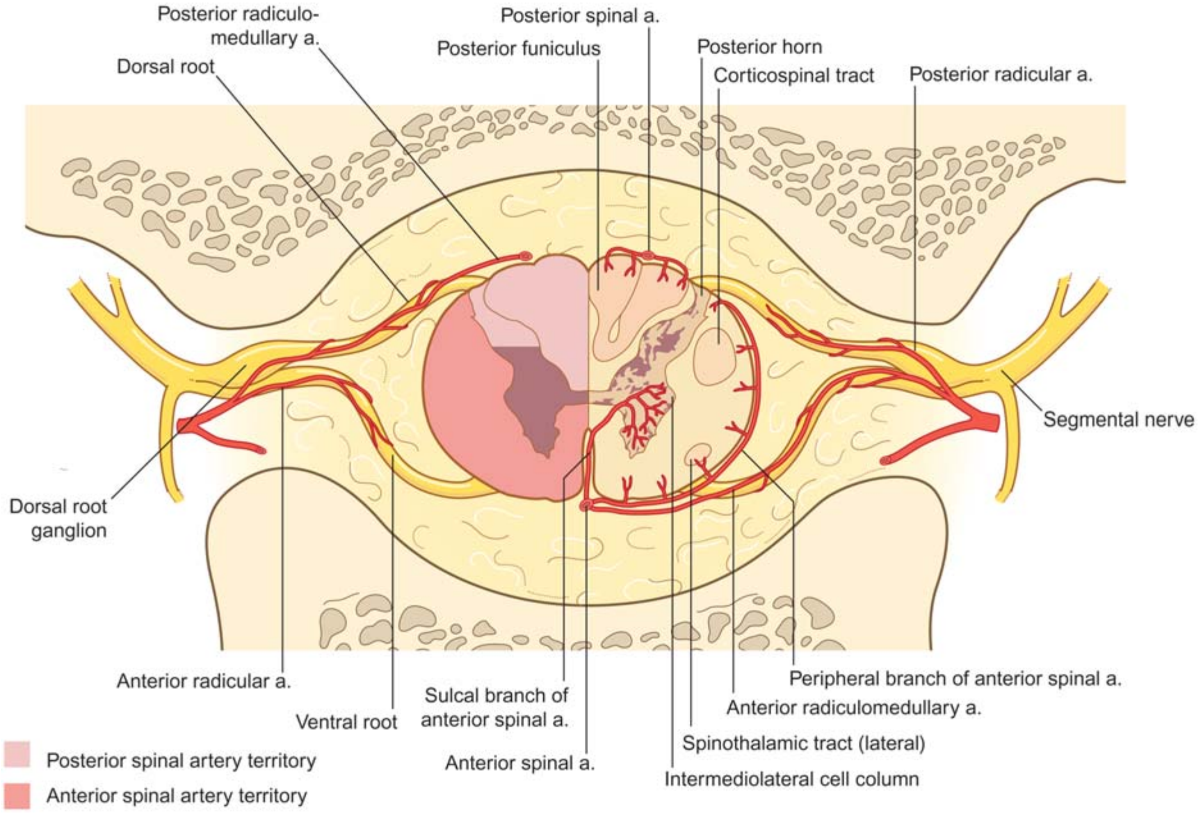
Posterior radiculo-medullary a.
Dorsal root
Posterior spinal a.
Posterior funiculus
Posterior horn
Corticospinal tract
Posterior radicular a.
Segmental nerve
Dorsal root ganglion
Anterior radicular a.
Ventral root
Sulcal branch of anterior spinal a.
Anterior spinal a.
Peripheral branch of anterior spinal a.
Anterior radiculomedullary a.
Spinothalamic tract (lateral)
Intermediolateral cell column
Posterior spinal artery territory
Anterior spinal artery territory

FIGURE 2-4 ■ Intrinsic blood supply of the spinal cord. The vascular territories are depicted on one side of the cord. The territory supplied by the posterior spinal arterial system is indicated. The rest of the spinal cord is supplied by the anterior circulation, with the darker region indicating the area supplied exclusively by the sulcal branches of the anterior spinal artery.

critical feeding vessels or by aortic hypotension. The resulting neurologic syndrome depends on the location of ischemic lesions along and within the spinal cord, which depends, in turn, on the vascular anatomy discussed previously. A wide variety of pathologic disturbances of the aorta result in spinal cord ischemia. As reviewed elsewhere,[1] they include both iatrogenic causes, such as surgery and aortography, and intrinsic aortic diseases, such as dissecting and nondissecting aneurysms, inflammatory aortitis, occlusive atherosclerotic disease, infective and noninfective emboli, and congenital coarctation. Spinal cord ischemia is a rare complication of pregnancy, possibly due to aortic compression, which can occur toward the end of gestation.

Some authors have suggested that the midthoracic region (T4 to T8) is particularly vulnerable to ischemia because of the sparseness of vessels feeding the anterior spinal artery in this region and its poor anastomotic connections. Others have stressed the vulnerability of the watershed areas between the three anterior spinal arterial territories. Although the concept is theoretically appealing, documentation of the selective vulnerability of these regions is not completely convincing. For example, a review of 61 case reports with respect to the distribution of ischemic myelopathies resulting from surgery on the aorta does not especially suggest that either of these areas is more vulnerable than other cord segments (Table 2-1).[1] Even when the operation was performed on the thoracic aorta (and thus the proximal clamp was placed above the midthoracic cord feeder), the lumbosacral cord segments were the site of the ischemic damage more often than the supposedly more vulnerable midthoracic segments (Table 2-1). Similarly, the watershed area between these two arterial territories (T8 to T9) does not seem particularly vulnerable. In fact, the most frequently affected cord segment within each vascular territory in these 61 cases was centrally placed—T6 in the midthoracic territory and T12 in the lumbosacral territory—rather than at the borders, as might be anticipated with watershed vulnerability (Fig. 2-5).

Moreover, of the 25 cases of spinal cord infarction in an unselected autopsy series of 300 cases, two-thirds were in cervical cord segments; the most commonly affected segment was C6. Such a distribution would be unexpected if either the midthoracic or the watershed area was particularly vulnerable. It may be that the poorly vascularized thoracic cord, which has much less gray matter than the cervical and lumbar enlargements, actually matches its sparse blood supply with its reduced metabolic requirements.[2]

The site of aortic disease also plays an important role in the location of the lesion along the spinal cord. For example, distal aortic occlusion often presents with lumbosacral involvement, whereas dissecting aneurysm of the thoracic aorta commonly presents with infarction in the midthoracic region. Similarly, cord ischemia following surgery on the abdominal aorta is essentially confined to the lumbosacral territory, whereas surgery on the thoracic aorta not infrequently involves the midthoracic segments (Table 2-1). Regardless of the pathologic process affecting the aorta, however, it generally involves the suprarenal portion if there is cord ischemia because the important radiculomedullary arteries usually originate above the origin of the renal arteries.

Ischemic spinal cord syndromes can be subdivided into several different categories including those with either bilateral or unilateral involvement restricted to the anterior or posterior spinal artery territories, those with involvement restricted to the central gray matter and, less commonly, those with a complete transverse myelopathy.

TABLE 2-1 ■ Influence of Location of Aortic Surgery on the Vascular Territory of Resulting Spinal Cord Ischemia

	Location of Surgery	
Vascular Territory of Ischemia	**Abdominal Aorta**	**Thoracic Aorta**
Cervical region (C1–T3)	0	0
Midthoracic region (T4–T8)	1	14
Lumbosacral region (T9–conus)	25	21

Based on 61 reported cases. From Goodin DS: Neurologic sequelae of aortic disease and surgery. p. 23. In Aminoff MJ (ed): Neurology and General Medicine. 4th Ed. Churchill Livingstone Elsevier, Philadelphia, 2008, with permission.

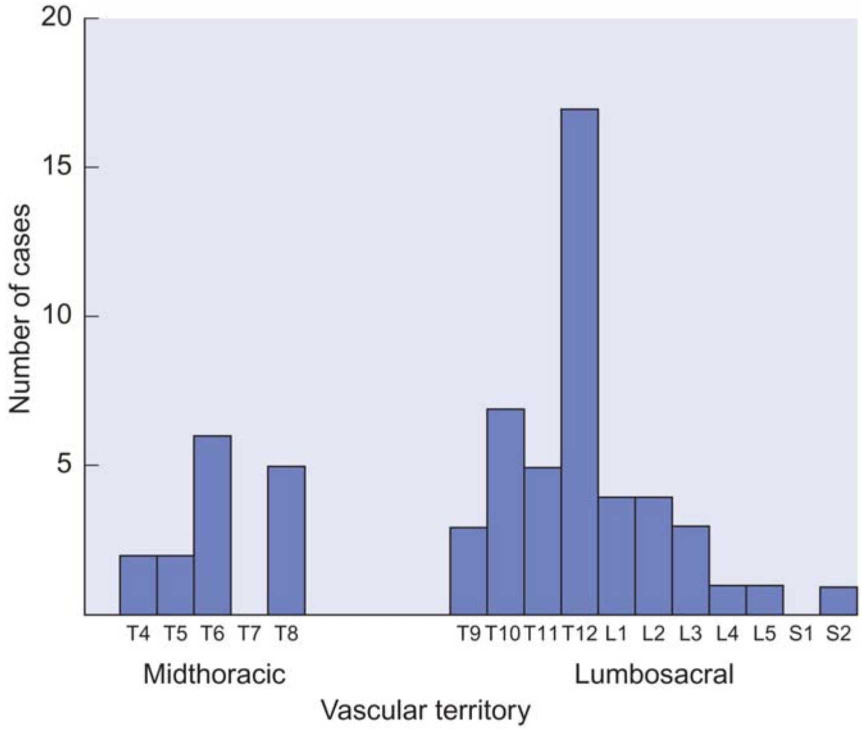

FIGURE 2-5 ■ Upper segmental level of spinal cord involvement in 61 cases of spinal cord ischemia after surgery on the aorta (based on previously published reports).

Anterior Spinal Artery Syndrome

Ischemic injury of the spinal cord at a particular segmental level may present with a complete transverse myelopathy. Within the spinal cord, however, there are certain vascular territories that can be affected selectively.[3] In particular, the territory of the anterior spinal artery, especially its sulcal branch, is prone to ischemic injury.[3] This increased vulnerability probably relates to two factors. First, the anterior circulation receives a much smaller number of feeding vessels than the posterior circulation. Second, the posterior circulation is a network of anastomotic channels and therefore probably provides better collateral flow than the single and sometimes narrowed anterior artery. The relative constancy of the resulting syndrome presumably reflects the relative constancy of the intrinsic vascular anatomy of the cord.

As mentioned earlier, the anterior spinal artery supplies blood to much of the spinal gray matter and to the tracts in the anterior and lateral white matter. Ischemia in this arterial territory therefore gives rise to a syndrome of diminished pain and temperature sensibility with preservation of vibratory and joint position sense. Weakness (either paraparesis or quadriparesis, depending on the segments involved) occurs below the level of the lesion and may be associated with other evidence of upper motor neuron involvement, such as Babinski signs, spasticity, and hyperreflexia. Bowel and bladder functions are affected, owing to interruption of suprasegmental pathways. Segmental gray matter involvement may also lead to lower motor neuron deficits and depressed tendon reflexes at the level of the lesion. Thus, a lesion in the cervical cord may produce flaccid areflexic paralysis with amyotrophy in the upper extremities, spastic paralysis in the lower extremities, and dissociated sensory loss in all limbs. In contrast, a lesion in the thoracic cord typically presents with only spastic paraplegia and dissociated sensory loss in the legs. The syndrome usually comes on abruptly, although occasionally it is more insidious and progressive. Occasionally, also, a transverse myelopathy can result from ischemia to the spinal cord.[3]

Motor Neuron Disease

On occasion, diseases of the aorta (e.g., dissecting aneurysms or atherosclerosis) that interfere with the blood supply to the anterior spinal artery result in more restricted cord ischemia. This may occur because of better anastomotic connections between the anterior and the posterior pial arterial plexuses in some individuals or because of greater vulnerability of the anterior horn cells with their greater metabolic activity. The ischemic injury in these circumstances is limited to the central gray matter supplied by the sulcal branches (Fig. 2-6). Clinical impairment is then confined to the motor system and is associated with amyotrophy. When the onset is abrupt, the ischemic nature of the lesion usually is apparent, but when the onset is more gradual, and especially when pyramidal signs are also present, it may mimic other diseases, such as amyotrophic lateral sclerosis or spinal cord tumors.

Posterior Spinal Artery Syndrome

In contrast to the anterior spinal artery syndrome, selective ischemia of the posterior circulation, characterized by prominent loss of posterior column function with relative sparing of other functions, is rarely recognized clinically and only occasionally reported pathologically.[4,5] For example, in two reviews of a total of 63 cases of nonsurgical spinal cord ischemia, only 7 (9%) had posterior spinal artery patterns.[3,4] The relative infrequency of this syndrome presumably relates to the more abundant feeding vessels

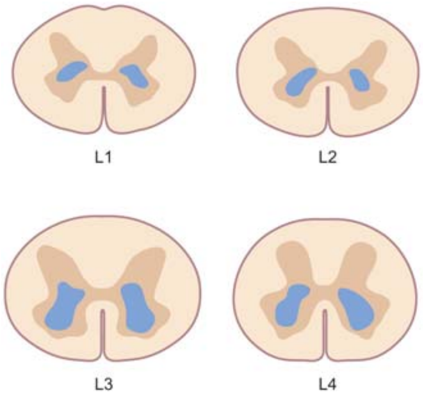

FIGURE 2-6 ■ Area of infarction within the spinal cord over four adjacent spinal segments in a patient reported by Herrick and Mills (Herrick MK, Mills PE: Infarction of spinal cord. Two cases of selective gray matter involvement secondary to asymptomatic aortic disease. Arch Neurol 24:228, 1971). The infarction was extensive but limited to the gray matter, particularly the anterior horns.

and better anastomotic connections in this arterial system compared to the anterior spinal artery.

Unilateral Cord Syndromes

In some cases, the area of ischemic damage can be confined to only a small portion of the spinal cord. For example, in the reviews cited previously,[3,4] 22 (35%) of the patients with nonsurgical spinal cord ischemia had unilateral syndromes involving either the anterior or posterior aspects of the spinal cord.

Intermittent Claudication

Intermittent claudication (limping) refers to a condition in which a patient experiences difficulty in walking that is brought about by use of the lower extremities. The evolution of concepts of intermittent claudication is of historical interest and is described elsewhere.[1] In brief, Charcot initially described this syndrome in 1858 and related it to occlusive peripheral vascular disease in the lower extremities. In 1906, Dejerine distinguished claudication caused by ischemia of the leg muscles from that caused by ischemia of the spinal cord. In the latter condition, the arterial pulses in the legs tend to be preserved, pain tends to be dysesthetic or paresthetic in quality and may not occur, and neurologic signs are frequently present, especially after exercise. In 1961, another form of neurogenic claudication was identified, caused by ischemia or compression of the cauda equina, which resulted from a narrowed lumbosacral canal (either congenital or due to degenerative disease). This condition is similar to that produced by ischemia of the spinal cord, but there are important differences. Thus, the sensory complaints tend to have a more radicular distribution, numbness and pain are aggravated by certain postures (e.g., lumbar extension when walking or standing) and relieved by other postures (e.g., lumbar flexion when riding a bike or sitting), and signs of cord involvement (e.g., Babinski signs) are not present.

The clinical distinction between various types of claudication, particularly between the two neurogenic varieties, is sometimes difficult. The cauda equina variety, however, is more common than the spinal cord form. Intermittent spinal cord ischemia, when it occurs, can be associated with intrinsic diseases of the aorta, such as coarctation or atherosclerotic occlusive disease although, more commonly, it is due to degenerative disease of the cervical and thoracic spine. Bony erosion through vertebral bodies from an abdominal aortic aneurysm with direct compression of the spinal nerve roots has also been reported to produce intermittent neurologic symptoms. The clinical details of the single reported case, however, are not sufficient to determine whether the symptoms resemble those of intermittent claudication.

Cerebral Ischemia

ANATOMY

The aortic arch gives rise to all the major vessels that provide blood to the brain, brainstem, and cervical spinal cord (Fig. 2-7). The first major branch is the innominate (brachiocephalic) artery, which subsequently divides into the right common carotid and right subclavian arteries. The latter artery subsequently gives rise to the right vertebral artery, which ascends through the foramina of the transverse processes of the upper six cervical vertebrae to join with its counterpart on the left and form the basilar artery. The basilar artery provides blood to the posterior fossa and posterior regions of the cerebral hemispheres. The second major branch of the aortic arch is the left common carotid artery, and the third is the left subclavian artery, which, in turn, gives rise to the left vertebral artery.

STROKES AND TRANSIENT ISCHEMIC ATTACKS

Diseases of the aortic arch, such as atherosclerosis, aneurysms, and aortitis as well as surgery on this segment of the aorta, may give rise to symptoms of cerebrovascular insufficiency, such as strokes or transient ischemic attacks (TIAs). A young woman has even been reported with a stroke secondary to an occlusion of the aorta that was associated with the use of birth control pills and recurrent venous thromboses.[1] Cerebral ischemia is produced either by occlusion of a major vessel or by embolization of atheromatous or other material to more distal arteries. The resulting neurologic syndromes are not specific for any disease process but depend on the location and duration of the vascular occlusion.

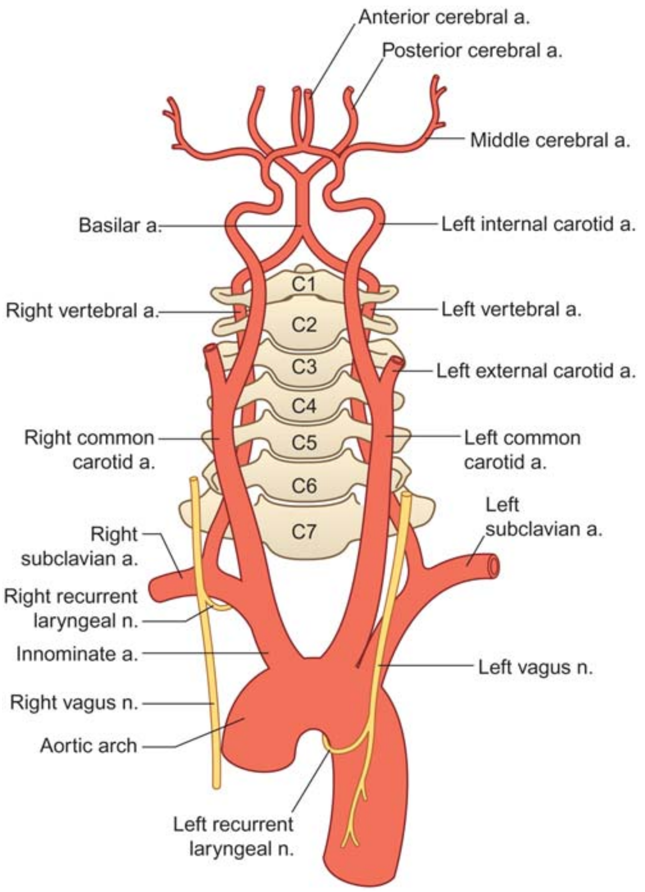
Anterior cerebral a.
Posterior cerebral a.
Middle cerebral a.
Basilar a.
Left internal carotid a.
C1
C2
C3
C4
C5
C6
C7
Right vertebral a.
Left vertebral a.
Left external carotid a.
Right common carotid a.
Left common carotid a.
Left subclavian a.
Right subclavian a.
Right recurrent laryngeal n.
Innominate a.
Left vagus n.
Right vagus n.
Aortic arch
Left recurrent laryngeal n.

FIGURE 2-7 ■ Vascular anatomy of the aortic arch and its branches.

Atherosclerosis

Atherosclerosis of the aortic arch and its branches, compared with atherosclerosis at the origin of the internal carotid artery, is an infrequent cause of stroke or TIAs, probably for two reasons. First, atherosclerosis is much less common in this location than at the carotid bifurcation (Table 2-2). Second, the anastomotic connections between the major vessels in the neck are extensive, and an occlusion at their origin from the aortic arch is therefore less likely to be associated with symptoms of ischemia than a more peripheral obstruction.

Transient Emboligenic Aortoarteritis

Transient emboligenic aortoarteritis has been reported by Wickremasinghe and colleagues to be a cause of stroke in young patients. They described 10 patients (aged 16 to 36 years), all of whom had presented with pathologically verified thromboembolic strokes, and 3 of whom had a history of TIAs preceding the event by as much as 4 years.[6] All these patients had both active and healed inflammatory lesions of the central elastic arteries, such as the aorta, innominate, common carotid, and proximal subclavian arteries. Active lesions were small (200 to 300 μm in diameter) and associated with a mural thrombus on the intimal surface. Healed lesions usually were associated with fibrous plaques but not with a mural thrombus. More peripheral arteries supplying the brain were normal. This condition seems to be distinct from segmental aortitis of the Takayasu type. Clinically it is an acute, intermittent disorder with an approximately equal sex incidence, whereas Takayasu disease is more chronic and has a strong female predominance. The systemic symptoms of Takayasu disease are absent, and occlusion of the central arteries does not occur in this condition.

TABLE 2-2 ■ **Distribution of Atherosclerosis in the Aorta and Its Branches**

Location	Number of Lesions
External carotid artery	9
Internal carotid artery	256
Common carotid artery	16
Innominate artery	16
Subclavian artery	29
Vertebral artery	55
Aortoiliac region	952
Femoropopliteal region	772

Based on data from Crawford ES, DeBakey ME, Cooley DA, et al: Surgical considerations of aneurysms and atherosclerotic occlusive lesions of the aorta and major arteries. Postgrad Med 29:151, 1961.

Subclavian (Cerebral) Steal

Disease of the aortic arch may result in occlusion of either the innominate artery or the left subclavian artery proximal to the origin of the vertebral artery. This, in turn, may result in the reversal of the usual cephalad direction of blood flow in the ipsilateral vertebral artery (Fig. 2-8), depending on individual variations in the collateral circulation, and may result in ischemia in the posterior cerebral circulation.[7] In some patients, this is particularly evident when the metabolic demand (and therefore the blood flow) of the affected arm is increased

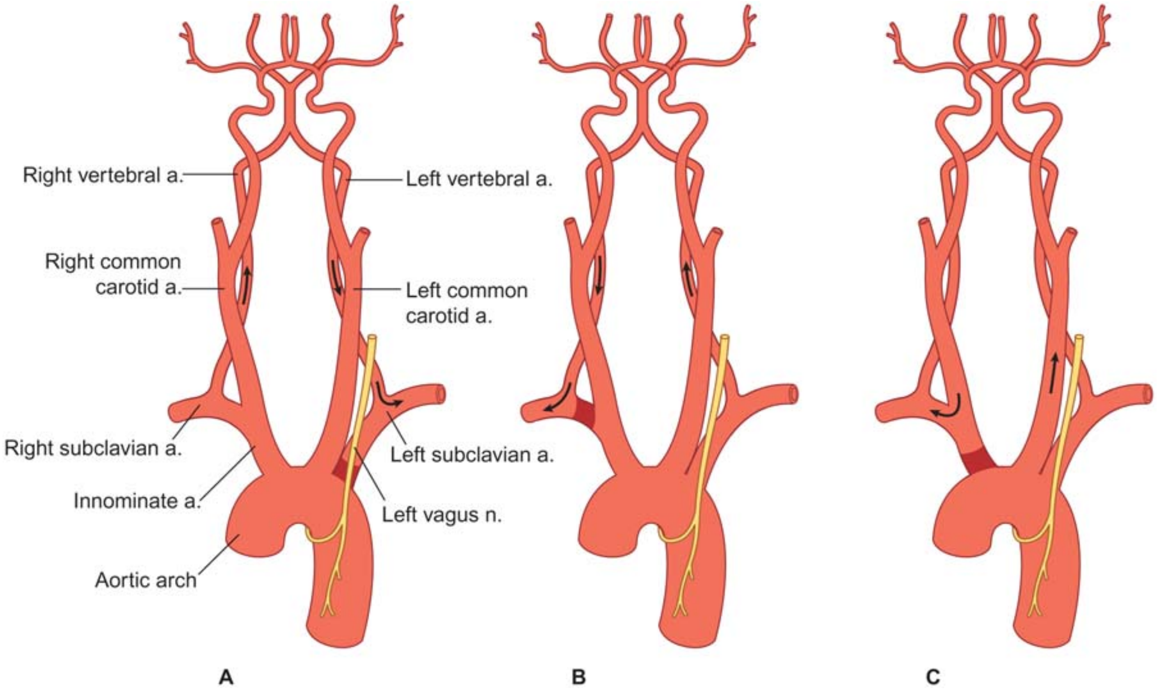

FIGURE 2-8 ■ Mechanisms producing subclavian steal syndrome in diseases of the aortic arch and its branches. *A*, Obstruction of the left subclavian artery at its origin, resulting in reversal of blood flow in the left vertebral artery. *B*, Obstruction of the right subclavian artery distal to the takeoff of the right common carotid artery, resulting in reversal of blood flow in the right vertebral artery. *C*, Obstruction of the innominate artery at its origin, producing reversal of blood flow in the right common carotid artery.

during exercise. If the innominate artery is blocked proximally, it may also cause a reversal of blood flow in the right common carotid artery, resulting in anterior circulation ischemia (Fig. 2-8).

Killen and colleagues reviewed the clinical features of a series of patients with demonstrated reversals of arterial blood flow in a vertebral artery (i.e., with flow from the vertebral artery into the ipsilateral subclavian artery).[8] The left subclavian artery was affected more than twice as often as the right subclavian and innominate arteries combined, probably as a result of the more frequent involvement of this artery by atherosclerosis (Table 2-2). Men were affected three times as often as women, probably reflecting the greater prevalence of atherosclerosis in men. Of the 87 patients in this series with symptoms that were adequately described, 75 (86%) had symptoms referable to the central nervous system (CNS). These symptoms were usually transient, lasting seconds to a few minutes, although the deficits were sometimes permanent. The neurologic manifestations of steal varied but most frequently included motor difficulties, vertigo, visual deficits, or syncope. Ischemic symptoms in the arms occurred in only a few patients, and precipitation of CNS symptoms by exercise of the arm ipsilateral to the occlusion was uncommon. Although reconstructive surgery relieved symptoms in most patients in this series,[8] the frequent failure of surgery to correct these nonspecific symptoms has led to a reassessment of the clinical importance of cerebral steal. Thus, when noninvasive techniques such as Doppler ultrasonography have been used to define the direction of blood flow in the great vessels in a large spectrum of patients with vascular disease, the majority (50 to 75%) of patients with documented subclavian steal are found to be asymptomatic, even when the steal is bilateral.[1,7] When symptoms do occur, they are suggestive of transient vertebrobasilar insufficiency in only 7 to 37 percent of patients with steal; the occurrence of infarcts in this vascular territory is distinctly rare.[1] For this reason, a review of the topic led to the conclusion that subclavian steal is actually a marker of generalized atherosclerotic disease and that it is rarely a cause for symptoms of cerebral ischemia.[9]

Nevertheless, a related syndrome, the coronary subclavian steal syndrome, seems well documented. This syndrome consists of angina (with or without posterior circulation symptoms such as vertigo) induced by upper limb exercise. It follows a coronary artery bypass graft using the left internal mammary artery in the setting of a hemodynamically significant subclavian stenosis.

Peripheral Neuropathy

The peripheral nervous system is sometimes affected by aortic disease or surgery. The syndromes produced may be the presenting manifestations of aortic disease and may mimic less life-threatening conditions.

MONONEUROPATHIES

Left Recurrent Laryngeal Nerve

The left recurrent laryngeal nerve descends in the neck as part of the vagus nerve and wraps around the aortic arch just distal to the ligamentum arteriosum (Fig. 2-7) before reascending in the neck to innervate all the laryngeal muscles on the left side except the cricothyroideus. It may be compressed by disease of the aortic arch, such as dissecting and nondissecting aneurysms or aneurysmal dilatation proximal to a coarctation of the aorta.[9] The resulting hoarse, low-pitched voice may be one of the earliest presenting symptoms of these conditions, although it is often overshadowed by other symptoms or signs, such as chest pain, shortness of breath, congestive heart failure, or hypertension.

Femoral Nerve

The femoral nerve arises from the nerve roots of L2, L3, and L4. It forms within the belly of the psoas muscle and then exits on its lateral aspect to innervate the quadriceps femoris, iliacus, pectineus, and sartorius muscles and the skin of the anterior thigh and medial aspect of the leg. The nerve is located considerably lateral to the aorta (Fig. 2-9) and hence is rarely involved by direct compression. It may, however, be compressed by a hematoma from a ruptured aortic aneurysm into the psoas muscle and thereby signal a life-threatening condition that requires an urgent operation.

The femoral nerve may also be injured as a consequence of aortic surgery. The mechanism of injury in such cases is presumed to be ischemic and related

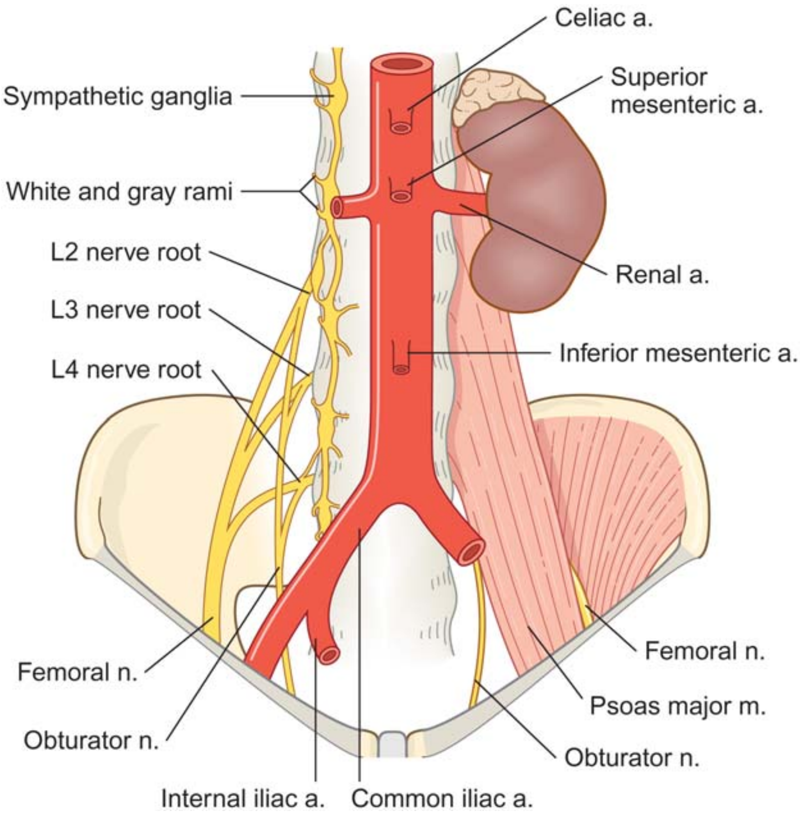

FIGURE 2-9 ■ Anatomy of the abdominal aorta showing its relationship to the femoral and obturator nerves, which form within the psoas muscle from branches of the L2, L3, and L4 segmental nerves.

to poor collateral blood supply to the intrapelvic portions of the femoral nerves.

Obturator Nerve

The obturator nerve also forms within the belly of the psoas muscle by the union of fibers from the L2, L3, and L4 segments, but, in contrast to the femoral nerve, exits medially from this muscle (Fig. 2-9). It innervates the adductors of the leg and the skin on the medial aspect of the thigh. It too is lateral to the aorta and not usually involved by direct compression. Like the femoral nerve (and often together with it), the obturator nerve may be compressed by a hematoma in the psoas muscle.

RADICULOPATHIES

Nerve roots, particularly L4, L5, S1, and S2, which lie almost directly underneath the terminal aorta and iliac arteries (Fig. 2-10), may be directly compressed by an aortic aneurysm in this region. The syndromes produced are typical of radicular disease, with unilateral radiating pain and a radicular pattern to the sensory and motor findings.

Radiculopathies may also be produced by erosion of one or more vertebral bodies by an aortic aneurysm, with consequent compression of the nerve roots in the cauda equina or at the root exit zones. The syndrome produced is not necessarily associated with back pain; it may result in multisegmental involvement on one side or even in paraplegia.[10]

POLYNEUROPATHIES

Ischemic Monomelic Neuropathy

Ischemic monomelic neuropathy was described in detail by Wilbourn and co-workers, who reported 3 patients (and alluded to another 11) who had a distal "polyneuropathy" in one limb after sudden occlusion of a major vessel.[11] One of their patients had a saddle embolus to the distal aorta that occluded the right common iliac artery, another had a superficial femoral artery occlusion after

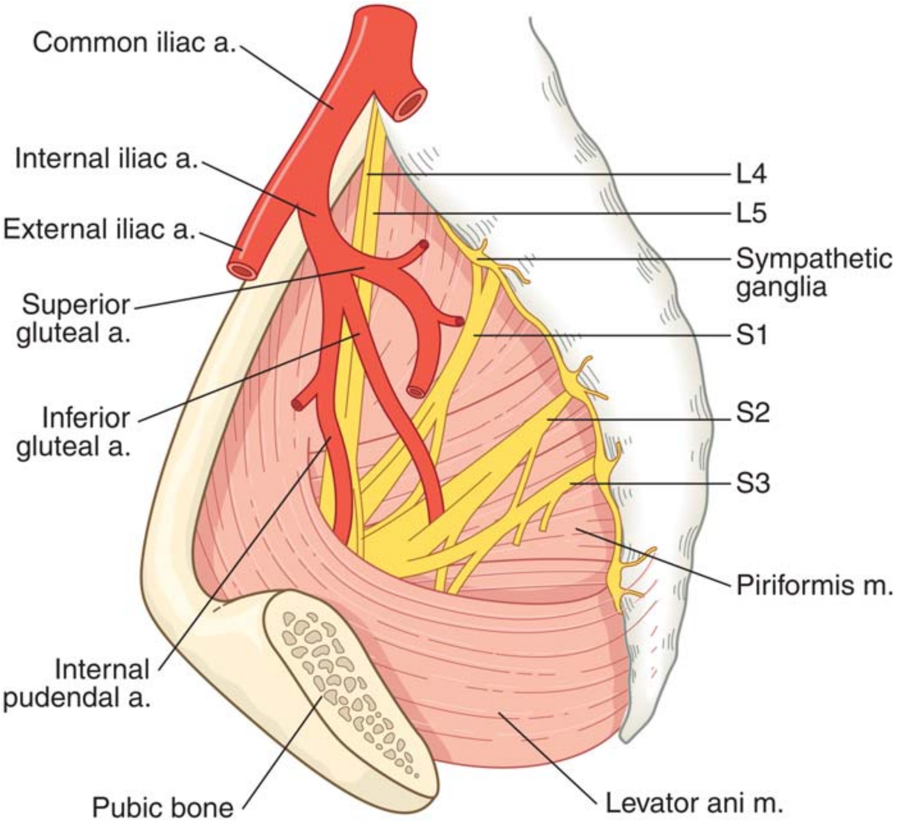

FIGURE 2-10 ■ Anatomy of the terminal branches of the aorta in relationship to the nerve roots that subsequently join to form the sciatic nerve. Aneurysmal dilatation of the abdominal aorta often includes dilatation of these branch vessels, which can compress the nerve roots, particularly the L4, L5, S1, and S2 nerve roots, which lie directly underneath.

placement of an intra-aortic balloon pump, and the third had upper extremity involvement. The syndrome consists of a predominantly sensory neuropathy with a distal gradient. It affects all sensory modalities and is associated with a constant, deep, causalgia-like pain. The symptoms persist for months, even after revascularization or without evidence of ongoing ischemia. The results of nerve conduction studies and needle electromyography suggest an axonal neuropathy. There is no evidence of ischemic muscle injury, such as induration, muscle tenderness, or elevated serum creatine kinase levels. Most recent reports of this condition seem to be as a complication of vascular access for dialysis, and the syndrome appears to be quite rare as a manifestation of aortic disease.

AUTONOMIC NEUROPATHIES

Anatomy

The autonomic nerves, particularly the lower thoracic and lumbar sympathetic fibers that lie close to the aorta and its branches, may be injured by disease of or surgery on the aorta. The preganglionic efferent sympathetic nerve fibers originate in the intermediolateral cell column in the spinal cord (Fig. 2-4) and exit segmentally between T1 and L2 with the ventral roots. The sympathetic fibers part company with the segmental nerves through the white rami communicantes (Fig. 2-2), which enter the paravertebral sympathetic ganglia and trunks to form bilateral sympathetic chains; these chains are situated lateral to and parallel with the vertebral column (Fig. 2-11). Some of these fibers synapse on postganglionic neurons in the ganglia of their segmental origin, whereas others ascend or descend in the trunk to different segmental levels before making such synapses. In the lumbosacral and cervical segments, where there are no white rami (i.e., below L2 or above T1), the segmental ganglia receive preganglionic contributions only from cord segments either above them (lumbosacral ganglia) or below them (cervical ganglia). The postganglionic fibers rejoin the segmental nerves through the gray rami communicantes (Fig. 2-2) to provide vasomotor, sudomotor, and pilomotor innervation throughout the body.

Some of the preganglionic fibers, in contrast, do not synapse in the paravertebral ganglia but pass through them to form splanchnic nerves, which then unite in a series of prevertebral ganglia and plexuses (many of which overlie the thoracic and abdominal aorta). These structures, in turn, provide sympathetic innervation to the viscera. The plexus that overlies the aorta in the region of its bifurcation, the superior hypogastric plexus (Fig. 2-11), is responsible (via the inferior hypogastric and other pelvic plexuses) for sympathetic innervation of the pelvic organs, including the prostate, prostatic urethra, bladder, epididymis, vas deferens, seminal vesicles, and penis in men (Fig. 2-12) and the uterus, bladder, fallopian tubes, vagina, and clitoris in women. This plexus is formed by the union of the third and fourth lumbar splanchnic nerves with fibers from the more rostral inferior mesenteric plexus. Its segmental contribution usually derives from T11 to L2.

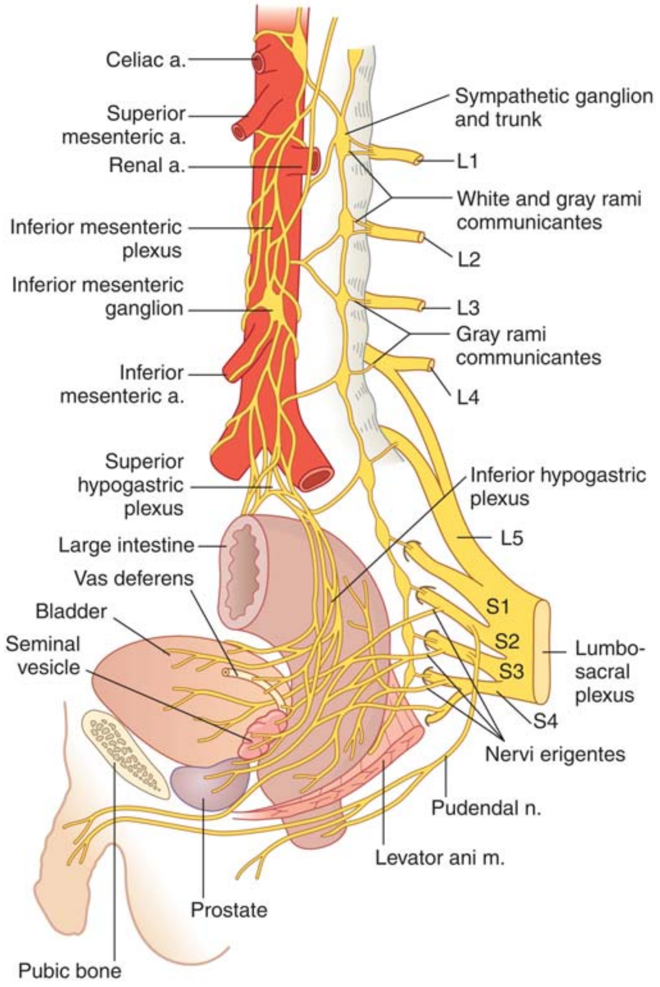
Celiac a.
Superior mesenteric a.
Renal a.
Inferior mesenteric plexus
Inferior mesenteric ganglion
Inferior mesenteric a.
Superior hypogastric plexus
Large intestine
Vas deferens
Bladder
Seminal vesicle
Pubic bone
Prostate
Levator ani m.
Pudendal n.
Nervi erigentes
S4
Lumbo-sacral plexus
S1
S2
S3
L5
Inferior hypogastric plexus
L4
Gray rami communicantes
L3
L2
White and gray rami communicantes
L1
Sympathetic ganglion and trunk

FIGURE 2-11 ■ Anatomy of the terminal aorta and pelvis in the male in relationship to the sympathetic and parasympathetic nerves in the region.

The visceral afferent fibers accompany the efferent autonomic fibers and pass uninterrupted back

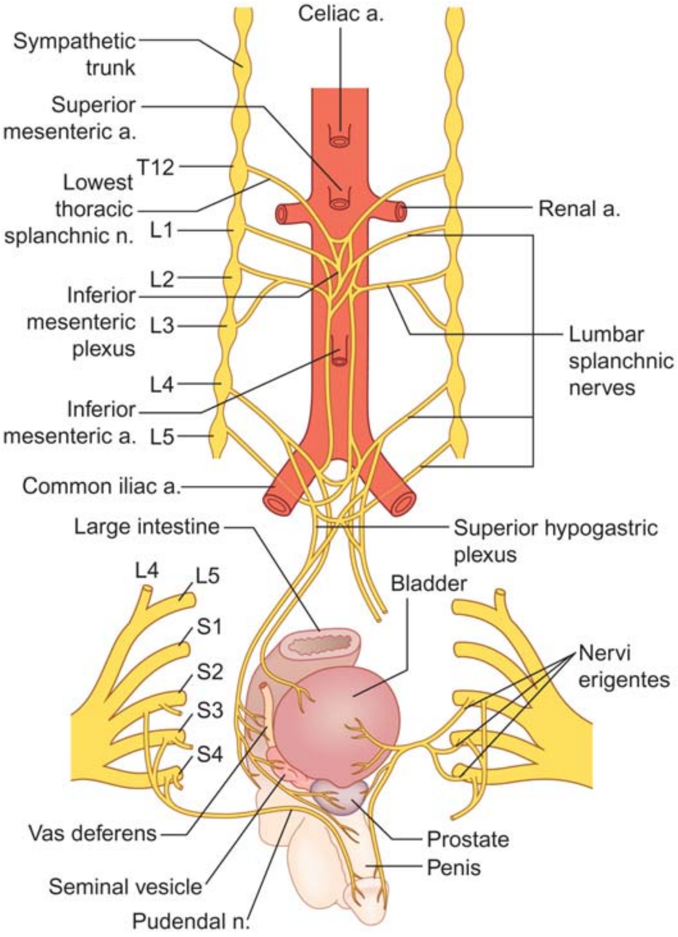

FIGURE 2-12 ▪ Distribution of sympathetic (*left*) and parasympathetic (*right*) nerves to the pelvic viscera and sexual organs in the male.

through the trunk, ganglia, and white rami to reach their nerve cells of origin in the dorsal root.

Postsympathectomy Neuralgia

Operations on the distal aorta to treat symptomatic aortic disease from atherosclerosis or other causes frequently include intentional sympathectomy as part of the effort to improve blood flow to the legs. This is usually done by dividing the sympathetic chain below the last white ramus at L2, thereby depriving the lower lumbar and sacral ganglia of their preganglionic innervation. Such an operation is often followed by a distinctive pain syndrome, termed *postsympathectomy neuralgia*. The syndrome occurs typically in patients in whom the sympathetic chain is interrupted at L3 by removal of the segmental ganglion. The pain is characterized as deep, boring, nonrhythmic, and nonradiating; onset is abrupt but delayed usually for several days. It is located predominantly in the thigh, either medially or laterally, and is associated with tenderness in the area of pain. The course is self-limited, with an average duration of 3 weeks.

Disorders of Sexual Function

Normal male sexual function has two distinct components. The first, erection, is a response mediated predominantly through the parasympathetic nervous system by the pelvic splanchnic nerves (nervi erigentes) arising from segments S2, S3, and S4 (Fig. 2-12). Activation of these nerves causes vasodilatation of the penile cavernosal artery and engorgement of the penile musculature and sinuses. The blood supply to the penis is provided by the internal pudendal artery via the internal iliac artery (Fig. 2-10). The sympathetic nervous system, however, must have at least a modifying influence on erection because bilateral sympathectomy may disturb it. By contrast, unilateral sympathectomy seems not to affect sexual function. The second component, orgasm and ejaculation, can be divided into two phases. The first phase, expulsion of seminal fluid into the prostatic urethra, is a response mediated predominantly by the sympathetic nervous system through the superior hypogastric plexus. A mucous-like liquid (preejaculate), which lubricates the ejaculation pathway, is added to the seminal fluid by paired bulbourethral (Cowper) glands, located inferior to the prostate. The second phase, orgasm and emission, is produced by the rhythmic (clonic) contraction of penile musculature (bulbocavernosus and ischiocavernosus) innervated by somatic (pudendal) nerves (Fig. 2-12).

Normal female sexual function is quite similar. During the first component of the response (arousal), blood flow to the clitoral, cavernosal, and labial arteries is increased, leading to elevation of clitoral intracavernous pressure, tumescence and protrusion of the clitoris, and engorgement and eversion of the labia minora. There is also vasodilatation and engorgement of the vaginal wall, which produces an increase in both its length and diameter and causes a transudation of plasma through the vaginal epithelium, thereby producing a lubricant for the inner vaginal surface during intercourse. Additional moistening is provided by secretions from the paired greater vestibular (Bartholin) glands, located slightly posterior to the vaginal opening and homologous to the Cowper glands in men. During the second component of the response (orgasm) there are rhythmic (clonic) contractions of the genitopelvic and anal smooth muscles.

Male sexual function may be disturbed by aortic disease or surgery. Female sexual function has not been as well studied in these circumstances, although it seems to be affected to a similar degree as in men. Because the superior hypogastric plexus lies close to the aortic bifurcation (Fig. 2-11), most preoperative and postoperative sexual disturbances occur with disease of this portion of the aorta and, in men, most involve ejaculation (Table 2-3). The pelvic splanchnic nerves are not situated near the aorta (Fig. 2-11) and usually are not affected by aortic disease or surgery. Disturbances in erection (arousal), however, do occur, possibly because of sympathetic dysfunction, a reduction in blood flow to the internal pudendal artery and penis, or cavernovenous leakage. To determine whether blood flow or sympathetic function was more important in this regard, Ohshiro and Kosaki examined the outcome of (1) terminal aortic operations either done traditionally or designed to spare the superior hypogastric plexus and (2) operations that did or did not preserve blood flow in the internal iliac arteries.[12] Their results indicated that preservation of the hypogastric plexus appeared to be more important for maintenance of normal erection and ejaculation than was preservation of blood flow in the internal iliac arteries (Table 2-4). Other authors have also found that modification of operative technique to spare the superior hypogastric plexus considerably improves postoperative sexual function.

Despite the importance of operative technique in preserving sexual function, preservation of blood flow is probably also important. Thus, Nevelsteen and colleagues reported a clear relationship between the occurrence of preoperative impotence and the adequacy of blood flow through the internal iliac arteries.[13] In this study, however, no special attempt was made to improve blood flow in the internal iliac artery during surgery, so that it is unclear whether a different operative approach might have been beneficial in restoring postoperative sexual function.

TABLE 2-3 ■ Male Sexual Dysfunction in Patients with Disease of or Surgery on the Aorta

Patient Status		Sexual Function	
Preoperative Status (All Patients)	Number of Patients	Normal (%)	Abnormal (%)
Iliac occlusion	22	82	18
Terminal aortic occlusion	10	40	60
Abdominal aortic aneurysm	12	83	17
Postoperative Status*		Impaired Ejaculation (%)	Impaired Erection (%)
Iliac occlusion	18	28	17
Terminal aortic occlusion	4	75	25
Abdominal aortic aneurysm	10	70	30

*All patients had normal preoperative sexual function.
Based on data from Ohshiro T, Takahashi A, Kosaki G: Sexual function in patients with aortoiliac vascular disorders. Int Surg 67:49, 1982.

TABLE 2-4 ■ Influence of Blood Flow and Sympathetic Function on Male Sexual Function After Abdominal Aortic Operations

		Postoperative Sexual Disturbance	
Parameter	Number of Patients	Ejaculation (%)	Erection (%)
Internal Iliac Blood Flow			
Bilaterally good	29	31	21
Unilaterally good	12	42	8
Bilaterally poor	4	50	25
Type of Surgery			
Classic	32	47	25
Nerve sparing	13	8	8

Based on data from Ohshiro T, Kosaki G: Sexual function after aortoiliac vascular reconstruction. J Cardiovasc Surg 25:47, 1984.

AORTIC DISEASES AND SURGERY

Certain conditions affecting the aorta merit special consideration because of the variety of nervous system syndromes that each can produce.

Aortitis

Injury to the aorta by a variety of infectious, toxic, allergic, or idiopathic causes may produce similar inflammatory pathologic changes in the elastic media

TABLE 2-5 ■ Causes of Aortitis

Stenosing Aortitis
Takayasu arteritis
Postradiation during infancy
Nonstenosing Aortitis
Syphilis
Mycobacterial infections
Other bacterial infections (e.g., *Salmonella* or *Staphylococcus*)
Human immunodeficiency virus infection
Mycotic aneurysms
Rheumatic fever
Rheumatoid arthritis
Giant cell arteritis
Collagen vascular and other diseases*
Ankylosing spondylitis
Relapsing polychondritis
Reiter syndrome
Behçet disease
Cogan syndrome

*Systemic lupus erythematosus, scleroderma, psoriasis, Crohn disease, and ulcerative colitis.

(Table 2-5). Such aortic damage may lead to neurologic syndromes either primarily through direct involvement of important branch arteries by the pathologic process or secondarily through the development of aneurysms, aortic stenosis, or atherosclerosis. The neurologic syndromes produced either primarily or secondarily by aortitis depend on both the nature and the location of the resulting aortic lesion.

SYPHILITIC AORTITIS

During the prepenicillin era, syphilis was a common cause of aortitis, although by the 1950s its occurrence had markedly declined. A report in 1958 on the relative occurrence of atherosclerotic and syphilitic thoracic aortic aneurysms showed cases of syphilis outnumbering atherosclerosis by a ratio of 1.3:1. A similar report published in 1982 gave this ratio as 0.13:1. The pathologic process in syphilitic aortitis is almost always in the thoracic aorta, in contrast to the distribution of atherosclerosis, which is more prevalent in the abdominal aorta (Table 2-2). The aortitis is accompanied by aneurysmal dilatation of the aorta in approximately 40 percent of cases. Rarely, it presents with multiple arterial occlusions and mimics Takayasu arteritis, although patients are generally older than those with Takayasu arteritis and are usually men.

TAKAYASU ARTERITIS

Takayasu arteritis is an idiopathic inflammatory condition affecting the large arteries, particularly the aorta and its branches.[14] The pathogenesis seems to involve cell-mediated autoimmunity, although the responsible antigen is unknown. The onset of disease is typically between the ages of 15 and 30 years, and the condition seems most prevalent in Asian and Hispanic populations.[14] More than 85 percent of affected individuals are women. In the early (prepulseless) phase, the disease may be characterized by systemic symptoms such as fever, night sweats, weight loss, myalgia, arthralgia, arthritis, and chest pain. In some patients, however, the systemic symptoms are either inconspicuous or absent. The later (pulseless) phase of the disease is characterized by occlusion of the major vessels of the aortic arch, producing symptoms such as Takayasu retinopathy, hypertension (secondary to renal artery stenosis, coarctation, or both), aortic regurgitation, and aortic aneurysms. Symptoms of cerebral ischemia can occur; however, they are typically reported in only a few patients. Nevertheless, a report from South Africa on 272 patients who were diagnosed with Takayasu arteritis, based on the criteria of the American College of Rheumatology, found that 20 percent of the cohort had symptoms of cerebrovascular disease, including TIAs and stroke.[15] In addition, 32 percent of this cohort experienced intermittent claudication of either upper or lower limbs. Seizures and headaches have also been reported but are uncommon. Involvement along the aorta is typically diffuse, although some patients (perhaps as many as 20%) present with symptoms related to more restricted aortic involvement.[14,15] The disorder is discussed further in Chapter 50.

GIANT CELL ARTERITIS

Giant cell arteritis (GCA) seems to be a particularly important cause of aortitis in the elderly; although it typically affects medium-sized vessels, as many as one-fourth or more of affected individuals have large-artery involvement. In a series of 45 patients undergoing aortic resection and who had microscopic evidence of active noninfectious aortitis, the majority had either unclassifiable aortitis (47%) or GCA (31%), two entities that were histopathologically indistinguishable.[16] The presenting symptoms in patients with GCA or unclassified aortitis are generally nonspecific and include exhaustion, night sweats, weight loss, chest and back pain, headache, fevers of unknown origin, TIAs, and arm claudication.[16] Typically, all segments of the aorta (ascending aorta, arch, and descending aorta) are involved in the inflammatory process, although involvement can be more restricted. Between 10 and 20 percent of patients with unclassified aortitis or GCA will subsequently develop either dissecting or, more commonly, nondissecting aortic aneurysms.

Aortic Aneurysms

NONDISSECTING ANEURYSMS

Nondissecting aortic aneurysms can be caused by any pathologic process that weakens the arterial wall, such as inflammation, infection, or atherosclerosis. In the past, syphilis was an important cause, but at present almost all these aneurysms are caused by atherosclerosis. As a result, the distribution of aortic aneurysms essentially parallels the distribution of atherosclerosis within the aorta, with most occurring in the abdominal aorta (Tables 2-2 and 2-6).

TABLE 2-6 ■ Distribution and Nature of Aortic Aneurysms

Site	Number of Cases
Nondissecting Aneurysms	
Aortic arch	56
Descending thoracic aorta	116
Thoracoabdominal aorta	25
Abdominal aorta	829
Dissecting Aneurysms	
Thoracic aorta	62

Based on data from Crawford ES, DeBakey ME, Cooley DA, et al: Surgical considerations of aneurysms and atherosclerotic occlusive lesions of the aorta and major arteries. Postgrad Med 29:151, 1961.

The incidence and prevalence of abdominal aortic aneurysms, which depend on age and sex, and are influenced by smoking history and hypertension, have declined since the 1990s both in Europe and the United States, as also has the prevalence of ruptured aneurysms. Since 1990, mortality rates from abdominal aortic aneurysms for both men and women have decreased in many developed countries.[17] The basis for this shift in natural history is unclear.

Disturbances of neurologic function in aortic aneurysms are uncommon, but when they occur, they are variable and depend in part on the location and extent of the lesion. Abdominal aneurysms may result in sexual dysfunction, compressive neuropathies, or, rarely, spinal cord ischemic syndromes, including intermittent claudication, asymmetric paraparesis, and paraplegia; descending thoracic aneurysms may produce spinal cord ischemia, and aortic arch aneurysms may result in cerebral ischemia or recurrent laryngeal nerve dysfunction. Most commonly, neurologic symptoms are produced by either rupture or direct compression. Even when aneurysms result in paraplegia, the neurologic deficit is often caused by bony erosion through the vertebral bodies and direct compression of the spinal cord or cauda equina rather than by ischemia.

DISSECTING AORTIC ANEURYSMS

Dissecting aortic aneurysms, in contrast to nondissecting aortic aneurysms, predominantly involve the thoracic aorta, either at the beginning of the ascending segment (type A) or immediately distal to the left subclavian artery at the aortic isthmus (type B). Their etiology has not been established. Atherosclerosis is probably not a major factor because atherosclerosis is seldom found in the region of the intimal tear because the distribution of these aneurysms along the aorta is unlike that of atherosclerosis and because atherosclerosis is only infrequently present. Nevertheless, hypertension probably is a factor as it is present in the large majority of patients with either type A or type B dissections. Moreover, dissecting aortic aneurysms have been associated with cystic medial necrosis, a degenerative condition focally affecting the arterial media, which may itself be related to hypertension. This condition is increased in patients with Marfan syndrome, as are dissecting aneurysms.

Most aneurysms, however, do not occur in patients with Marfan syndrome or other identifiable collagen disorders, and the pathophysiology remains unknown. It has been estimated that 60 percent of thoracic aortic aneurysms involve the aortic root or ascending aorta, 10 percent the arch, 40 percent the descending thoracic aorta, and 10 percent the thoracoabdominal aorta.[18] More than 95 percent of thoracic aortic aneurysms are asymptomatic and their prevalence (prior to rupture or dissection) has been estimated to be greater than 0.16 to 0.34 percent.[18] There may be a familial tendency for their occurrence and, for larger aneurysms (> 6 mm), the 5-year survival may be as low as 50 percent.[18] Neurologic involvement from dissecting aneurysms (due to the cut-off of important arteries by the dissection or by embolization) is well described but uncommon. It occurs more frequently with type A than type B dissections, and it usually involves either spinal or cerebral ischemia. Neurologic involvement may also occur during surgery to repair the aneurysm. Patients with aortic dissection usually present with acute chest or back pain, which generally leads to the proper diagnosis. On occasion, however, pain is absent, and the neurologic syndrome is the presenting feature. Moreover, the neurologic deficit produced by the dissecting aneurysm is sometimes only transient, lasting for several hours, and thereby mimicking other transient disturbances of neurologic function.

TRAUMATIC AORTIC INJURY

Brutal deceleration injuries to the chest, especially from motor vehicle accidents, may result in traumatic rupture of the thoracic aorta, often just distal to the left subclavian artery at the aortic isthmus (i.e., the slight constriction of the aorta at the point where the ductus arteriosus attaches). Many of these patients die immediately, but some present with an acute paraplegia. Still others have a chronic aortic aneurysm that may present years later with acute spinal cord ischemia or other neurologic symptoms. Some patients with traumatic aortic injury have a less critical condition (e.g., limited intimal flaps) and may not warrant immediate surgical treatment. Nevertheless, they will still need to be monitored closely for signs of progression that would prompt urgent intervention.

Coarctation of the Aorta

Coarctation of the aorta, a relatively common congenital condition, typically results in constriction of the thoracic aorta just distal to the origin of the left subclavian artery. Less commonly, it occurs as part of Takayasu arteritis, and this condition should be suspected if the location of the coarctation is atypical. It may also follow radiation exposure during infancy; in these cases, the pathologic process is focal and limited to the segment of aorta that was in the field of irradiation. Coarctation can result in a variety of neurologic symptoms (Table 2-7). Cerebral infarcts probably result from embolization of thrombotic material in the dilated aorta proximal to the obstruction.

Subarachnoid hemorrhage from ruptured saccular aneurysms can occur with coarctation. In the general population, aneurysmal hemorrhage has an annual incidence of approximately 8 per 100,000 and rarely occurs before the age of 20 years. Accordingly, the reported occurrence of ruptured aneurysms in 2.5 percent of patients with coarctation of the aorta suggests an association of these two disorders, although the coincidental occurrence of the two conditions cannot be completely excluded.

Headache is a common accompaniment of coarctation, perhaps as a result of secondary hypertension, but, again, the incidental occurrence of two unrelated conditions cannot be excluded.

TABLE 2-7 ■ Neurologic Sequelae of Coarctation of the Aorta*

Sequela	Incidence (%)
Ruptured intracerebral aneurysms	2.5
Ischemic stroke during childhood	1.0
Neurogenic intermittent claudication†	7.5
Headache	25.0
Episodic loss of consciousness	3.0
Intracerebral hemorrhage‡	<1.0
Spinal cord compression‡	<1.0

*Based on a review of 200 patients with coarctation of the aorta. Tyler HR, Clark DB: Neurologic complications in patients with coarctation of aorta. Neurology 8:712, 1958.

†Patients with exercise-induced motor or sensory disturbances in the lower extremities.

‡These complications were not found in the series reported by Tyler and Clark but have been reported by others, as described elsewhere.[1]

Episodic loss of consciousness may occur in patients with coarctation of the aorta. It may result either from syncope due to associated cardiac abnormalities or from seizures. It is unclear, however, whether seizures unrelated to cerebrovascular disease are more prevalent in these patients than in the general population.

Neurogenic intermittent claudication can result from aortic coarctation. In patients with coarctation of the aorta, blood flow to the legs is often provided by collateral connections between the spinal arteries and the distal aorta. In these situations, the blood flow through the radiculomedullary and intercostal arteries distal to the obstruction is reversed, and the exercise-related spinal ischemia may be related to "steal" by the increased metabolic demands (and thus increased blood flow) of the legs rather than aortic hypotension distal to the coarctation (Fig. 2-13). These collaterals are sometimes so extensive that they cause spinal cord compression and mimic (clinically and radiologically) vascular malformations of the spinal cord. Spinal cord injury can rarely follow surgical repair of a coarctation, and this complication may be delayed by several months following the repair.

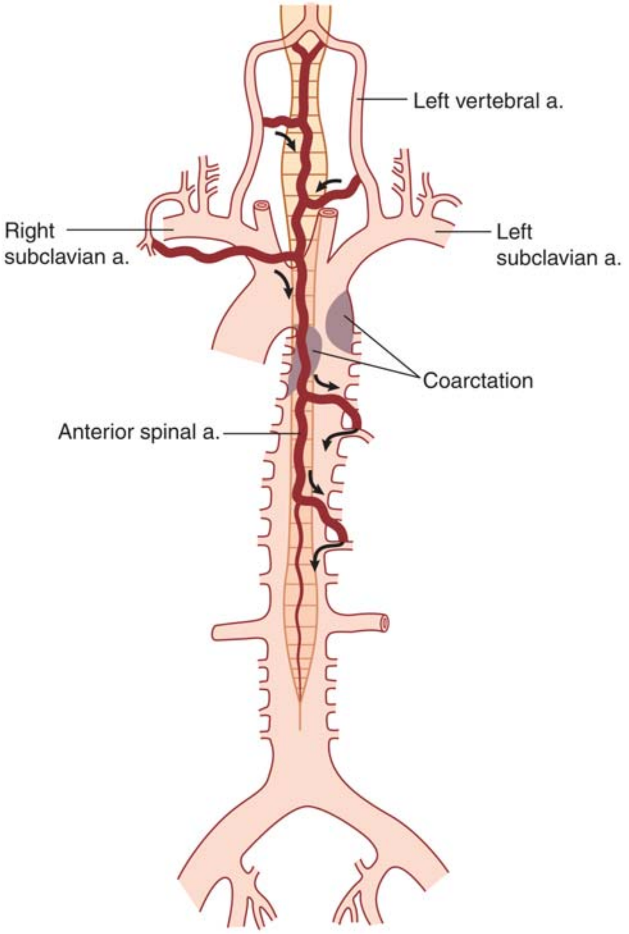

FIGURE 2-13 ■ Mechanism of steal in coarctation of the aorta. Obstruction of the aorta at the isthmus causes dilatation of the anterior spinal artery and reversal of blood flow in anterior radiculomedullary arteries distal to the obstruction. In this circumstance, the blood flow to the lower extremities is provided by these (and other) collaterals, and use of the lower extremities may cause shunting of blood from the spinal circulation to the legs, which, in turn, sometimes results in spinal cord ischemia.

Surgery and Other Procedures

AORTIC SURGERY

As with diseases of the aorta, the risks of aortic surgery depend in part on the site of operation. Thus, operations on the aortic arch may produce cerebral ischemia either by intraoperative occlusion of major vessels or by embolization of material such as calcified plaque loosened during surgery. Operations on the suprarenal aorta may result in spinal ischemia, whereas operations on the distal aorta may result in sexual dysfunction or ischemia of the femoral nerve.

The major complication of all aortic operations, however, is intraoperative spinal cord ischemia with resultant paraplegia or paraparesis. The occurrence of this complication varies with the location of the surgery and the nature of the pathologic process affecting the aorta (Table 2-8). Thus, operations on dissecting or nondissecting aortic aneurysms that are entirely abdominal are associated with a lower incidence of this complication than operations on aneurysms confined to the thoracic aorta. Surgery on aneurysms involving the entire abdominal and thoracic aorta carries the highest risk of producing cord ischemia. Operations on the distal aorta for occlusive disease only rarely result in spinal ischemia, especially when confined to the infrarenal portion. This variability presumably occurs because important feeding arteries to the spinal circulation are more likely to be ligated during surgery, included within the segment of the aorta that is cross-clamped, or subjected to distal hypotension when the aortic lesion is above the level of origin of the renal arteries.

Operations on the thoracic aorta for coarctation are much less frequently complicated by spinal ischemia than thoracic operations done for other reasons.

TABLE 2-8 ■ Spinal Cord Ischemia During Surgery and Procedures on the Aorta

Diagnosis	Number of Patients	Percentage with Spinal Cord Damage
Nondissecting aortic aneurysm		
Abdominal	1,724	0.46
Thoracic	585	6.3
Thoracoabdominal	102	21.6
Dissecting aortic aneurysm	102	30.4
Abdominal aortic occlusion	1,089	0
Coarctation of aorta	12,532	0.41
Aortography	17,949	0.01

From Goodin DS: Neurologic sequelae of aortic disease and surgery. p. 23. In Aminoff MJ (ed): Neurology and General Medicine. 4th Ed. Churchill Livingstone Elsevier, Philadelphia, 2008, with permission.

There are probably at least two reasons for this difference. First, the former patients are younger, and the extent of overall arterial disease is therefore less. Second, as mentioned earlier, the flow in the radiculomedullary vessels below the coarctation is frequently reversed, so obstruction of blood flow in them (either by ligation or cross-clamping the aorta above and below their origin) may actually result in an increased blood supply to the spinal cord.

Aortography and Other Procedures on the Aorta

Aortography may be associated with either spinal or cerebral ischemia, depending on the portion of the aorta visualized. This complication, however, is distinctly rare (Table 2-8). Paraplegia may also occur during intra-aortic balloon assistance after myocardial revascularization.

Intraoperative Adjuncts to Avoid Spinal Cord Ischemia

Several adjuncts are commonly used during surgery in an attempt to avoid spinal cord injury. They include the use of hypothermia and maintenance of mild intraoperative hypertension in addition to thiopental anesthesia and/or the administration of naltrexone and intraoperative corticosteroids, all of which are thought to reduce the metabolic requirements of the spinal cord or otherwise enhance tolerance to ischemia. In addition, many authors have reported that minimization of cross-clamp time results in a lower incidence of spinal ischemia.

Other adjunctive methods such as the reattachment of intercostal arteries, the use of shunts to maintain distal perfusion pressure, and the use of cerebrospinal fluid drainage have not proved consistently effective at preventing spinal cord ischemia, although the more recent experience with such adjunctive techniques has been quite favorable.[19] Part of the difficulty with these procedures may relate to the extreme variability of the blood supply to the spinal cord. For example, if a crucial spinal artery leaves the aorta within the cross-clamped section, the preservation of distal blood flow is irrelevant. Furthermore, because the important intercostal arteries are few and unpredictably situated, the random reattachment of a few intercostal arteries may be fruitless. Spinal cord ischemia can also be delayed and occur hours to days following the aortic operation. In these circumstances, the maintenance of mild hypertension coupled with the use of supplemental oxygen and cerebrospinal fluid drainage may mitigate the consequences.

There has been considerable interest in the use of somatosensory evoked potentials (SEPs) and motor evoked potentials (MEPs) for assessing spinal cord function during operations on the aorta. The combined use of SEPs and MEPs may ultimately prove better than either technique alone, and, indeed, the most recent reports with both techniques have been encouraging. An approach that seems particularly valuable is the use of intraoperative MEPs or SEPs to identify those vessels that perfuse the spinal cord and therefore need reattachment, should not be sacrificed, or should not be included within the aortic cross-clamp. Another approach that has been reported to be useful is the use of intraoperative MEPs to monitor patients and to quickly increase both the distal aortic pressure and the mean arterial pressure in response to a drop in MEP amplitude. Nevertheless, although these reports are encouraging, the best method of monitoring intraoperative spinal cord function and how best to use the information to alter the operative technique so that postoperative spinal cord function is maintained are yet to be determined.

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CHAPTER

3

Neurologic Complications of Cardiac Surgery

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NEUROLOGIC SEQUELAE OF CORONARY ARTERY BYPASS GRAFTING
  Stroke After Coronary Artery Bypass Grafting
  Nonstroke Neurologic Complications After Coronary Artery Bypass Grafting
NEUROLOGIC SEQUELAE OF EXTRACORPOREAL CIRCULATION
  Neurologic Complications of Extracorporeal Membrane Oxygenation
NEUROLOGIC SEQUELAE OF CARDIAC VALVULAR SURGERY
PREOPERATIVE PREVENTION OF NEUROLOGIC COMPLICATIONS
NEUROLOGIC SEQUELAE OF CARDIAC TRANSPLANTATION

Cardiac surgery, including coronary artery bypass grafting (CABG), extracorporeal circulation, and aortic valve replacement, has the potential to significantly improve patients' functional status and reduce mortality; however, neurologic complications of surgery can limit and even eradicate these potential benefits. Perioperative and postoperative central and peripheral nervous system injury, especially stroke and delirium, can lead to permanent disability and hinder recovery from surgery. These complications can prolong hospitalization stay and increase the risk of medical complications and mortality. Identification of high-risk patients, enactment of preventive measures, and early recognition of reversible neurologic injury remains challenging but an important problem for both the cardiac surgical team and the consulting neurologist.

NEUROLOGIC SEQUELAE OF CORONARY ARTERY BYPASS GRAFTING

Although there has a been a decline in the number of CABG procedures in the United States over the last decade, due to an increase in percutaneous revascularization procedures, it remains one of the most commonly performed major surgical procedures, with approximately 400,000 operations done annually per year. CABG involves the use of autologous arteries and veins as grafts to bypass partially or completely obstructed coronary arteries affected by atherosclerotic disease. The most commonly used bypass conduits are the left internal thoracic artery and the greater saphenous vein, with left internal thoracic artery grafts to the left anterior descending coronary artery in particular associated with higher long-term patency rates and clinical outcomes. The heart is usually arrested during the grafting procedure, necessitating the use of a cardiopulmonary bypass machine, which then provides perfusion pressure (including cerebral perfusion) and oxygenation during the typical 1 to 2 hour period of cardiac arrest. Due to an increased frequency of percutaneous revascularization and more recently developed minimally invasive grafting options—which often do not require cardiopulmonary bypass—patient selection for CABG is rigorous, with major considerations involving coronary artery anatomy, extent of disease, prior failed procedures, and medical comorbidities.[1]

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Stroke After Coronary Artery Bypass Grafting

The rate of stroke in patients undergoing CABG has decreased over the past few decades, with most series reporting a rate of less than 2 percent.[1] Clinically silent stroke detected by magnetic resonance imaging (MRI) may occur at a higher rate, and often these strokes are multifocal. A large single-center review of more than 40,000 patients found that the rate of stroke decreased over a 30-year span despite increasing patient risk profile.[2] When stroke does occur, it leads to a significant increase in hospital mortality, prolongs length of stay in the intensive care unit and the hospital, results in significant disability, and typically requires inpatient rehabilitation or nursing home placement at the time of hospital discharge.

In patients with acute neurologic symptoms concerning for stroke, brain imaging is important to rule out alternative etiologies and to help elucidate the etiology of stroke and overall burden to inform prognosis for neurologic recovery. Ischemic stroke following cardiac surgery is usually the result of either emboli or hypoperfusion. Watershed infarction occurs at the border zone between major cerebral arteries and often involves the subcortical white matter on MRI scans; it is suggestive of stroke due to hypoperfusion and is a common pattern of ischemia in patients who were exposed to decreased cerebral perfusion. Embolic stroke is often related to emboli from the heart or proximal aorta and is typically multifocal on imaging, involving all vascular territories. Although patients in the postoperative period following CABG are not candidates for systemic intravenous thrombolysis therapy, given the advent of extended windows for endovascular therapy it is important to pursue computed tomography (CT) angiography to identify large-vessel occlusions and facilitate thrombectomy discussions with a local stroke center.

Intracerebral hemorrhage is rare after CABG but may necessitate urgent medical and surgical treatment and decompression. It can occur during cardiopulmonary bypass due to effects on platelet adhesion and coagulation factors, but it most commonly occurs due to hemorrhagic conversion of an area of cerebral infarction. Rarely, cardiopulmonary bypass is complicated by pituitary apoplexy resulting from acute hemorrhage or infarction of an unrecognized pituitary adenoma during surgery; patients awaken with headache, ptosis, visual impairment, and ophthalmoplegia and may require transsphenoidal surgical decompression.

Intraoperative stroke represents between 30 and 50 percent of all strokes associated with CABG, and about half of these events are felt to be due to hypoperfusion. A decrease of mean arterial pressure of more than 10 mmHg is an important predictor of watershed strokes, and a prolonged cardiopulmonary bypass time exceeding 2 hours is associated with a higher rate of stroke.

Thromboembolic stroke also occurs intraoperatively and is related to specific surgical factors. For example, manipulation of the aorta during cannulation and cross-clamping can lead to dislodgement of atheroma or calcium. Studies using ultrasound to detect cerebral emboli have noted increased frequency of emboli during these moments of aortic manipulation. Stroke also occurs at higher frequency when valvular heart surgery is combined with CABG due to the additional risk of cerebral macroemboli associated with removal or repair of diseased heart valves. There have been multiple studies comparing the risk of stroke between "off pump" CABG techniques, wherein cardiopulmonary bypass machines were not used, compared to "on pump" CABG, and the overall results are conflicting, with rates likely varying due to differences in patient selection and preoperative risk factors.[2–4] Less common causes of embolic stroke include surgical complications such as air emboli, which can propagate into the cerebral vasculature and often present with focal stroke symptoms, encephalopathy, or seizures.

The majority of postoperative strokes following CABG occurs during the first 7 days after surgery. New-onset postoperative atrial fibrillation occurs in up to 30 percent of patients following CABG, especially within the first 3 days, and is associated with a higher risk of stroke. Low cardiac output after CABG is also associated with stroke due to hypoperfusion. After the first week, patients post-CABG remain at higher risk for stroke although this is largely related to a greater risk for thromboembolic events due to comorbidities such as older age, hypertension, diabetes mellitus, dyslipidemia, peripheral vascular disease, higher rates of chronic atrial fibrillation, and the need for further revascularization procedures.[2–4]

Ischemic complications following CABG can lead to visual disorders and symptoms. Retinal abnormalities on examination are common after CABG, including multifocal areas of retinal nonperfusion and cotton wool spots or retinal emboli; these findings are usually not associated with diminished visual acuity. Much less common, but more likely to cause visual impairment, is ischemic optic neuropathy. Anterior ischemic optic neuropathy due to infarction of the optic nerve head is associated with monocular, painless, and often permanent visual impairment along with optic disc swelling on examination. Visual testing may reveal central scotoma or altitudinal deficits. Retrobulbar or posterior ischemic optic neuropathy is rare and is often seen after a period of hypoperfusion; it is due to infarction of the intraorbital nerve and presents with acute blindness, which can be bilateral, without optic disc swelling on fundoscopic examination. The presence of a homonymous visual field deficit or cortical blindness (associated with normal pupillary and retinal examination) should prompt urgent imaging to evaluate for occipital lobe injury. Similarly, gaze deviation or gaze paralysis in the postoperative setting may suggest brainstem or hemispheric stroke.

Nonstroke Neurologic Complications After Coronary Artery Bypass Grafting

Encephalopathy is common after CABG surgery, occurring in between 10 and 30 percent of patients, and has a variety of etiologies. Delirium, an acute disorder of fluctuating attention and confusion, is more common in patients older than 65 years, and is associated with prolonged hospital length of stay and complications following surgery. Patients may present with hyperactive agitation, visual hallucinations, confusion, or hypoactive states. Aside from older age, preoperative risk factors for the development of delirium after cardiac surgery include baseline neurocognitive dysfunction, a history of prior stroke, a history of depression, baseline renal dysfunction, and a low serum albumin level. Postoperative associations with delirium include the need for mechanical ventilation for more than 24 hours, prolonged operating time, postoperative stroke, worsening renal function, and the use of benzodiazepines.[5] Onset of encephalopathy should also prompt an appropriate diagnostic work-up to rule out and correct inciting factors such as multifocal stroke, metabolic disorders including sodium disturbances and hypoglycemia due to excess insulin and decreased nutritional states around the time of surgery, and systemic infection including pneumonia and urinary tract infection.

Encephalopathy presenting as persistent coma is rare but usually suggests severe neurologic dysfunction with a poor neurologic prognosis. The most common causes include a large burden of stroke (usually involving the brainstem or bilateral cerebral hemispheres) or global hypoxic ischemic injury. The latter is often due to dysrhythmia, mechanical injury to the heart, or frank cardiac arrest.[5]

Seizures occur in up to 1 percent of patients after cardiac surgery including CABG and may be due to acute or recent stroke, metabolic derangements, hypoxic ischemic brain injury, or exposure to medications including high-dose tranexamic acid, procainamide, and lidocaine. Unrecognized alcohol dependence or inadvertent cessation of chronic medications such as benzodiazepines or anticonvulsants in the perioperative period may also cause seizures due to withdrawal. Seizures without clear tonic-clonic or focal motor manifestations may be difficult to recognize and patients may present with prolonged alteration in mental status or subtle findings such as intermittent gaze deviation or nystagmoid movements. As such, evaluation with electroencephalography can be valuable in the encephalopathic postoperative patient.

Peripheral nervous system complications after CABG are often related to mechanical factors leading to compression or stretch injury of nerves adjacent to the surgical field or those that are susceptible due to patient positioning factors. Brachial plexopathy has been reported to occur after cardiac surgery in 1 to 5 percent of patients who undergo median sternotomy. The lower trunk is the most commonly involved and clinically may mimic an ulnar neuropathy; the loss of the triceps reflex on the affected side helps distinguish plexopathy from a more peripheral lesion. There is usually weakness of intrinsic hand muscles, sensory loss or pain over the medial hand, and rarely, Horner syndrome. Risk factors include sternal retraction, direct trauma due to first rib fracture, and adducted arm position. Deficits usually reverse within 1 to 3 months, but may lead to more prolonged and permanent disability in some patients. Intraoperative electrophysiologic monitoring of sensory nerve conduction may help to detect and predict postoperative nerve injury and potentially allow for adjustment of intraoperative factors to decrease the incidence and severity of injury. Prevention strategies including more precise midline sternotomy, more caudal placement of retractors, avoiding asymmetric retraction, and maintaining neutral head and arm abduction positioning with appropriate cushioning, may help reduce the frequency of brachial plexopathy.[6]

Unilateral phrenic nerve injury, leading to hemidiaphragmatic paralysis, occurs in over 10 percent of patients after open-heart surgery. The left phrenic nerve lies along the pericardium between the lung and the mediastinal aspect of the pleura, making it particularly vulnerable to injury from manipulation and the effects of topical hypothermia related to cold cardioplegia. Although unilateral phrenic nerve injury may increase the risk of respiratory complications and atelectasis, the overall morbidity is generally low, and patients often experience recovery by around 6 months. Bilateral phrenic nerve injury is a much more rare complication and leads to prolonged mechanical ventilation.[6]

Less common mononeuropathies relate to injury of the recurrent laryngeal nerve and saphenous nerve. Similar to phrenic nerve injury, complications of internal thoracic artery dissection in combination with topical hypothermia can be associated with recurrent laryngeal nerve injury; patients present with hoarseness, ineffective cough, and aspiration when severe. Harvesting of the saphenous vein for CABG can lead to saphenous nerve injury, leading to decreased sensation, hyperesthesia, and pain along the medial lower leg.[6]

Although not unique to cardiac surgery, there is also growing recognition of surgery as a risk factor for development of acute inflammatory demyelinating polyradiculoneuropathy as a cause of postoperative quadriparesis and respiratory failure. Critical illness polyneuropathy and myopathy may develop in patients whose postoperative course has been complicated by sepsis, multi-organ failure, and prolonged use of paralytic medications or steroids. It can lead to difficulty weaning from mechanical ventilation and a higher risk of complications related to immobility in the hospital.

Neuropsychologic studies of cognitive function before and after CABG have identified both a short-term early cognitive decline immediately after surgery and a later-onset decline about 3 to 5 years after surgery. The early decline is usually reversible on the order of weeks or a few months, and is often associated with delirium during hospitalization. Similar short-term declines have also been reported in patients who underwent noncardiac surgery, suggesting that exposure to anesthesia may contribute to symptoms in vulnerable patients, and formal studies with serial neuropsychologic testing up to 1 year after CABG have showed that cognitive changes over this time are similar compared to patients who received percutaneous coronary intervention; therefore, common pretreatment cardiac and cerebrovascular disease and vascular risk factors likely also contribute to development of symptoms.[1,5,7]

Later-onset cognitive decline was found in up to 40 percent of patients after CABG at long-term follow-up 5 years after surgery when performance on cognitive testing was compared to baseline testing. At that time, it was assumed not only that late cognitive decline was common, but also that it was due to "on pump" cardiopulmonary bypass time in particular and the delayed effect of diffuse microemboli exposure during CABG. However, these initial studies lacked both unoperated patients with coronary artery disease and healthy patient control comparison groups. Subsequent studies shows that this delayed cognitive decline is not specific to patients who had "on pump" CABG. There are no significant differences in cognitive function 3 years after surgery in patients who had CABG with and without cardiopulmonary bypass, patients with nonsurgically treated coronary artery disease, and healthy controls; at 6 years, all three groups with coronary artery disease showed a similar degree of cognitive decline that was greater than the healthy control group. Studies of patients treated "on pump" and "off pump" during CABG showed no difference in cognitive performance 5 years after surgery. Taken together, there is no clear evidence that cardiopulmonary bypass is the major contributor to this observed late cognitive decline.[1,7]

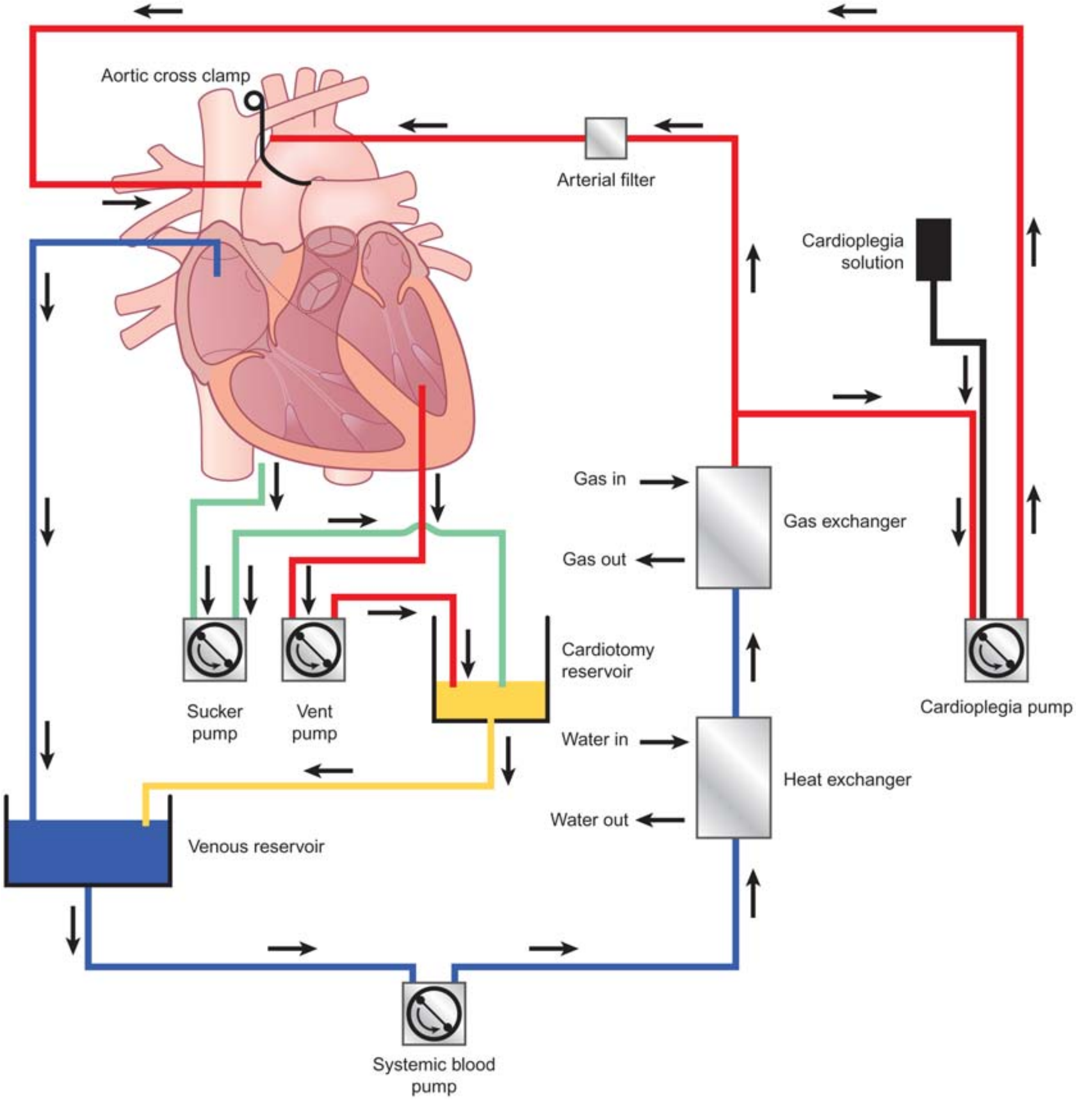
It therefore seems that preoperative cerebrovascular disease is more closely associated with the risk of delayed onset cognitive decline, due to a slow accumulation of ischemic brain injury related to ongoing vascular risk factors. Patients who had brain MRI scans showing evidence of prior cerebral ischemia before CABG have been found to have higher risk of subsequent cognitive decline. These findings highlight the importance of medical control of vascular risk factors to potentially reduce the risk of slow cognitive decline in this patient population.[7]

NEUROLOGIC SEQUELAE OF EXTRACORPOREAL CIRCULATION

The introduction of cardiopulmonary bypass over 70 years ago was the crucial development that led to modern cardiac surgery. However, it is associated with neurologic complications that are related to the procedure itself and which increase in likelihood as its duration is extended. Over the last decade, there has been a marked increase in the use of extracorporeal membrane oxygenation (ECMO), which allows for more prolonged cardiopulmonary support in patients with refractory respiratory or cardiac failure, and this patient population is at high risk for neurologic complications including ischemic stroke, cerebral hemorrhage, and hypoxic-ischemic brain injury.

For open-heart surgery, cardiopulmonary bypass requires cannulation of the ascending aorta and vena cava or right atrium, with drainage of venous blood to a reservoir which is then pumped through a membrane oxygenator and then routed via a filter to a cannula of the aortic arch (Fig. 3-1). The procedure requires clamping and cannulation of the aorta, which can lead to dislodging of atheromatous material in a diseased aorta and cause cerebral ischemia via embolization. Similarly, the high-velocity or turbulent blood flow from the end of the cannula can also lead to embolization of atheroma. As atherosclerotic disease is exceedingly common in patients with coronary artery disease, especially in patients over the age of 70, identification of aortic atheroma with intraoperative transesophageal echocardiography or epiaortic ultrasound may help dictate surgical planning.[8]

Extracorporeal circulation is facilitated by systemic heparinization and hemodilution, as the exposure



Aortic cross clamp
Arterial filter
Cardioplegia solution
Gas in
Gas out
Gas exchanger
Cardiotomy reservoir
Sucker pump
Vent pump
Water in
Water out
Heat exchanger
Cardioplegia pump
Venous reservoir
Systemic blood pump

FIGURE 3-1 ■ Schematic of an extracorporeal circulation circuit used in cardiopulmonary bypass surgery. (Modified from Machin D, Allsage C: Principles of cardiopulmonary bypass. Contin Educ Anaesth Crit Care Pain 6:176, 2006 with permission from Oxford University Press.)

to bypass circuits leads to a prothrombotic systemic inflammatory response. As such, anticoagulation is used to prevent thrombus formation, and hemodilution helps reduce blood viscosity. In addition, hypothermia is often used for neuroprotection during cardiac bypass for surgery, and it is recommended that rewarming occur slowly, with care to avoid temperatures above 37°C in order to prevent secondary neurologic injury; this is felt to be of particular importance in patients with known cerebrovascular disease prior to surgery. Evidence-based intraoperative guidelines for heart surgery with cardiopulmonary bypass have been published with an aim of minimizing risk of brain ischemia. One set of guidelines is summarized in Table 3-1.[8]

TABLE 3-1 ■ Evidence-Based Cardiopulmonary Bypass Practices that May Improve Neurologic Outcome

Practice	Class/Level of Evidence*	Mechanism
Arterial filtration	Class I/Level A	Minimize emboli
Intraoperative aortic imaging	Class I/Level B	Identify aortic plaque
	Class IIb/Level B	Reduce emboli
Minimize direct reinfusion of pericardial suction blood	Class I/Level B	Reduce emboli and prothrombotic systemic inflammatory response
Process and filter pericardial suction blood before reinfusion	Class IIb/Level B	
Alpha-stat pH management	Class I/Level A	Maintain metabolic coupled cerebral blood flow
Limit arterial line temperature to 37°C during rewarming	Class IIa/Level B	Avoid brain hyperthermia
Reduce blood contact with nonbiocompatible surface of cardiopulmonary bypass circuits	Class IIa/Level B	Reduce prothrombotic systemic inflammatory response
Maintain normal perioperative glucose levels	Class I/Level B	Avoid hyperglycemia
Reduce hemodilution	Class I/Level A	Avoid very low hematocrit

*Class I—Procedure or treatment should be performed. Class IIa—Reasonable to perform procedure or treatment; additional focused studies needed. Class IIb—Consider procedure or treatment; additional broad studies needed. Level A—Recommendation derived from multiple randomized studies. Level B—Recommendation derived from single randomized or multiple nonrandomized studies.

Neurologic Complications of Extracorporeal Membrane Oxygenation

Analogous to cardiopulmonary bypass for cardiac surgery, ECMO is increasingly used for the management of severe cardiac or respiratory failure, affording longer-term cardiopulmonary support either as a bridge to other therapies or to allow more time for recovery when conventional therapies are unsuccessful. Venous drainage usually occurs from the inferior vena cava or right atrium with extracorporeal oxygenation performed via artificial membranes. Oxygenated blood is returned via the femoral artery or ascending aorta in venoarterial (VA) ECMO which is often used for cardiogenic shock and cardiac failure as a bridge to recovery, ventricular assist device insertion, or cardiac transplantation. Venovenous (VV) ECMO involves return of blood through the superior vena cava, and is often used for respiratory failure due to infection, interstitial lung disease, or aspiration. The use of ECMO has dramatically increased over the last decade following worldwide influenza pandemics, but mortality and morbidity remain high, with neurologic complications being associated with particularly high mortality.[9]

Exact estimates of the rates of neurologic complications are challenging across series of ECMO patients given variable definitions and methodologies for detection, but overall they seem to be underestimated and occur in at least 10 to 15 percent of cases. In general, neurologic complications are reported more frequently with VA ECMO compared to VV ECMO, and although the mortality of patients on ECMO is already high due to the severity of the underlying disease state, mortality is substantially higher in patients who develop neurologic complications on ECMO compared to those who do not, approaching 100 percent in some series. Complications are more common in patients with pre-ECMO pyrexia, hypoglycemia, and need for inotropes, and also in patients whose ECMO indication is cardiac arrest or shock. Rapid correction of severe hypercapnia due to respiratory failure has also been implicated as a contributor to neurologic complications due to resultant cerebral vasoconstriction and impairment of cerebral autoregulation.[9,10]

Intracerebral hemorrhage is the most frequent neurologic complication associated with ECMO, with reports ranging from 5 to 10 percent of all patients, and it also carries the highest mortality, ranging from 90 to 100 percent. Risk factors for intracerebral hemorrhage include female sex; renal dysfunction and need for dialysis; coagulopathy including thrombocytopenia and decreased fibrinogen levels; and prolonged duration of mechanical ventilation and ECMO. Mechanistically, the need for anticoagulation likely contributes to the risk of hemorrhage and hematoma expansion after onset, but changes in cerebral vascular tone and hemorrhagic conversion of ischemic tissue are also key factors contributing to the high rate of hemorrhage. The systemic inflammatory response that is initiated when blood contacts ECMO circuitry also leads to an increased risk of hemorrhage. Treatment including reversal of anticoagulation, surgical decompression, and hematoma evacuation, has not been shown to clearly impact the high rates of mortality or permanent disability.[9,10]

Ischemic stroke is the second most common neurologic complication for patients on ECMO. Data regarding the most likely patterns or size of ischemic strokes are lacking, but mortality approaches 50 percent in multiple patient series. Disease-related risk factors include underlying coagulopathy, atrial fibrillation, and decreased cardiac output and hypotension, while ECMO-specific factors include impaired cerebral vascular autoregulation and embolic disease related to clots or air within the extracorporeal system. The rate of ischemic stroke is higher in VA ECMO as blood is returned directly into the arterial system. There are reports of successful acute treatment of large-vessel occlusion with mechanical thrombectomy in patients on ECMO but this intervention requires rapid detection and diagnosis of acute stroke which can be difficult in these patients who often require sedation while on ECMO. Spinal cord ischemia has also been reported in patients on ECMO, often when patients also require an intra-aortic balloon pump.[9,10]

Other neurologic complications include seizures, which may be related to cerebral hypoxia, focal hemorrhage, or stroke. Patients on ECMO are also at risk for peripheral nerve injury including compressive neuropathies during cannulation (depending on the site), secondary nerve injury if ECMO is complicated by local limb compartment syndrome or limb ischemia, or from prolonged static positioning and immobility. Femoral and sciatic neuropathy can occur with proximal leg vascular access in particular. Global cerebral hypoxic ischemic encephalopathy and brain death are commonly reported in patients with neurologic injury on ECMO.

Prevention of neurologic injury is challenging given that many of these risk factors are not easily modifiable. Avoidance of atheromatous segments of arteries during cannulation can help reduce procedure-related stroke, and care should be taken to avoid a rapid reduction of carbon dioxide. Anticoagulation goals can be adjusted and lowered in particularly high-risk patients. Mobility programs can be used to avoid prolonged immobility and to help prevent compressive neuropathies. As some acute neurologic processes such as large-vessel occlusion or seizures can be treated and reversed, it is also important to develop protocols to ensure daily neurologic examination with interruption of sedation and neuromuscular blockade to allow for detection of injury. Electroencephalograpic monitoring may be helpful, especially to look for nonconvulsive seizures. MRI is usually not possible with patients on ECMO, so CT imaging should be performed when there are concerns for acute cerebral injury. In the future, other biomarkers such as near-infrared spectroscopy monitoring of cerebral oxygen saturation and serum testing for markers of neuronal injury such as glial fibrillary acidic protein and neuron-specific enolase may be used more routinely to help guide hemodynamic parameters, identify changes due to acute neurologic injury, and prognosticate the degree of cerebral injury and recovery potential.[9,10]

NEUROLOGIC SEQUELAE OF CARDIAC VALVULAR SURGERY

Symptomatic severe aortic stenosis is associated with progressive congestive heart failure and exertional dyspnea, syncope, and angina, and carries a high mortality if not treated. Valve repair or replacement is considered definitive treatment and should be considered for patients with symptomatic stenosis and asymptomatic patients with imaging evidence of severe stenosis and either decreased cardiac output or symptoms on exercise testing; it should also be considered in those who are undergoing other cardiac surgery or those with very severe stenosis alone who are simply felt to be at low surgical risk.

Surgical aortic valve replacement classically involves sternotomy and open-heart surgery with cardiopulmonary machine bypass, similar to CABG. Transcatheter aortic valve replacement (TAVR) has become an established and increasingly frequent treatment alternative to surgical repair and involves a transfemoral, transapical, or transaortic catheter approach with endovascular placement of a balloon-expandable valve device to replace the native diseased valve. The decision regarding surgical versus transcatheter valve replacement is made by a multidisciplinary clinical team and involves assessment of surgical risk, risk of mortality and likelihood of improvement of quality of life, anatomic features of the aortic valve and vascular system, age of the patient, and the need for other cardiac surgery.

Surgical valve replacement is often preferred in younger patients, those with lower surgical risk, those who need mechanical valves, and those with specific anatomic considerations that require an open-heart approach. The rate of ischemic stroke in the early postoperative period (less than 30 days) is around 1 to 5 percent for isolated aortic valve surgery, and the risk is increased if valve surgery is combined with CABG. Surgical repair carries the risk of gas emboli from the release of intracardiac air and the procedure requires adequate de-airing and clearing of blood surrounding the aortic root, atria, and ventricles. Life-long anticoagulation is needed after mechanical valve placement for stroke and systemic embolus prevention, usually with a goal for an international normalized ratio of 2.5 to 3.5. Bioprosthetic valve embolus prevention often includes 1 year of aspirin and anticoagulation, followed by aspirin alone.[11]

Early trials involving TAVR in high-risk surgical patients revealed a higher rate of ischemic stroke in the early post-procedure period compared to surgical replacement. However, more recent trials have shown either no difference in the stroke rate or lower early stroke rates following TAVR, a difference that has been attributed to more precise neurologic injury detection methods compared with previous trials as well as presumed technical improvements in devices and delivery systems.[11] Trials have also demonstrated similar rates of stroke events up to 1 year after the procedure. The rate of stroke is highest in the immediate post-procedural time window (usually the first 48–72 hours), and the vast majority of strokes are thromboembolic in nature. Strokes occurring after 30 days involve hemorrhagic events in a quarter of patients. Periprocedural stroke after TAVR is often secondary to catheter wire manipulation or advancement of devices through an atherosclerotic aortic arch, root, or calcified aortic valve. Balloon post-dilation aortic insufficiency after TAVR can also increase risk of embolic stroke.[11,12]

Stroke after surgical valve replacement and TAVR is associated with an increased mortality and decreased quality of life. Efforts to reduce the risk of stroke after TAVR have included the use of cerebral embolic protection devices during the procedure, various different antiplatelet (monotherapy versus dual therapy) or anticoagulant strategies, preprocedure imaging evaluation of vascular structures to help with catheter advancement planning, and technical improvements reducing aortic manipulation time.[12] A retrospective cohort of over 100,000 patients who received TAVR between 2011 and 2017, however, found that there was no change in the rate of stroke at 30 days after the procedure, staying at around 2 percent over the time period. Additional strategies to lower rates of stroke after TAVR remain an active area of research.[13]

Nonstroke complications after TAVR include encephalopathy and seizures. One trial found that the rate of encephalopathy was up to 8 percent in patients following surgical valve replacement compared to 2 percent in patients after TAVR.[12] Patients who have undergone aortic stenosis surgery are also at risk for hyperperfusion injury to the cerebrum due to preoperative impaired cerebral autoregulation and a post-procedure sudden increase in cardiac output; patients may present with focal neurologic deficits or global encephalopathy, often due to intracerebral hemorrhage or seizures. Careful and tight control of post-procedure blood pressure can potentially reduce the risk of both hyperperfusion injury and hypotensive-related ischemia.

PREOPERATIVE PREVENTION OF NEUROLOGIC COMPLICATIONS

Identification and modification (when possible) of preoperative risk factors that place patients at higher risk of neurologic complications is an important part of the cardiac surgery evaluation and treatment plan (Table 3-2). Older age is associated with a higher rate of neurologic complications after CABG, with risk increasing with every decade of life. Preoperative history of hypertension, diabetes mellitus, tobacco smoking, and dyslipidemia are independently associated with risk of stroke following CABG and efforts should be made to address these risk factors prior to surgery when possible. Preoperative statin and beta-blocker initiation may reduce the risk of postoperative stroke, and the latter may also potentially reduce the rate of postoperative atrial fibrillation. Early postoperative use of aspirin decreases ischemic complications after surgery.[4,7]

Prior stroke or transient ischemic attack (TIA) is also a risk factor for postoperative stroke, and

TABLE 3-2 ■ Risk Factors for Cerebral Ischemia During Cardiac Surgery

Preoperative
Older age > 70 years[4]
Hypertension[7]
Diabetes mellitus[4,7]
Smoking[4]
History of cerebrovascular disease[4,7]
Atheromatous aorta[7]
Peripheral vascular disease[4,7]
Previous cardiac surgery[7]
Carotid stenosis, symptomatic[7]
Intraoperative
Prolonged cardiopulmonary bypass[4]
Combined coronary artery bypass and valvular surgeries
Large hemodynamic fluctuations[7]
Aorta cannulation and manipulation[7]
Postoperative
Atrial fibrillation[4,7]

timing of CABG or cardiac surgery following stroke depends on many factors including the size of the cerebral infarct and the urgency of cardiac intervention. Modern preoperative evaluation includes stroke risk assessment tools that account for the above factors, which can then be used to decide the most appropriate intervention for an individual patient (e.g., CABG versus percutaneous coronary revascularization) as well as technical operating factors (e.g., strategy for aortic manipulation and cannulation in a patient with identified atherosclerotic disease).

Symptomatic carotid stenosis, defined as a patient having a TIA or stroke in the distal circulation of an ipsilateral extracranial internal carotid artery with significant stenosis based on imaging criteria, is associated with a higher rate of stroke in patients undergoing CABG, although the mechanism of stroke is not usually related to carotid disease itself. Consensus clinical society guidelines note that in patients over the age of 65 and in those with left main coronary stenosis, peripheral vascular disease, a history of cigarette smoking, a history of stroke or TIA, or a carotid bruit on examination, it is reasonable to screen patients for carotid stenosis with duplex ultrasound screening prior to elective CABG surgery (Class IIa recommendation). In those who have greater than 80 percent carotid stenosis and have experienced ipsilateral retinal or hemispheric cerebral ischemic symptoms within 6 months of the planned surgery, carotid revascularization via carotid endarterectomy or carotid artery stenting before or concurrent with myocardial revascularization surgery is reasonable (Class IIa recommendation). In patients with asymptomatic carotid stenosis, even if severe, the safety and efficacy of carotid revascularization before or concurrent with myocardial revascularization are not well established (Class IIb recommendation).[14]

There is a lack of clear clinical trial data to definitively guide decisions about carotid revascularization technique and timing in preparation for cardiac surgery. However, expert recommendations suggest that carotid revascularization should be considered in patients with recently symptomatic carotid stenosis (50 to 99% in men, 70 to 99% in woman), bilateral asymptomatic carotid stenosis of 80 to 99 percent, or in unilateral asymptomatic stenosis of 70 to 99 percent when the contralateral vessel is 100 percent occluded. Choice of carotid stenting versus carotid endarterectomy may depend on numerous patient-specific factors including operative risk, but since stenting requires dual antiplatelet therapy after the procedure, it is not the ideal choice in patients with urgent indication for CABG given the higher risk of bleeding complications. As a result, endarterectomy may be a more favorable choice in patients with urgent indications for CABG. Carotid stenting prior to CABG has been associated with a lower risk of neurologic complications in some series compared to patients receiving combined endarterectomy with CABG, and this sequential strategy can be considered in patients who can wait longer for coronary revascularization procedure.[14]

NEUROLOGIC SEQUELAE OF CARDIAC TRANSPLANTATION

As with all cardiac surgery, cardiac transplantation for patients with end-stage cardiac failure refractory to medical therapy can substantially prolong life and decrease mortality. However, neurologic complications can significantly limit these potential benefits. In a series of over 300 patients who received cardiac transplantation, a perioperative neurologic complication occurred in nearly one-fifth of patients, most commonly encephalopathy and delirium followed by cerebrovascular complications.[15] Complications such as encephalopathy and peripheral nervous system disorders were often reversible, but cerebrovascular complications were associated with unfavorable functional outcome at 1 year after transplant. Follow-up occurred for up to 18 years and, over this time frame, there was an incidence of neurologic complications approaching 80 percent, most commonly sleep disorders, depression, and polyneuropathy. Cerebrovascular events occurred at a higher rate than in the general population over this follow-up period, with higher rates of intraparenchymal hemorrhage in particular. Central nervous system infections were uncommon, but were predictive of mortality.[15] For a more detailed discussion regarding neurologic complications after heart transplantation, see Chapter 44.

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CHAPTER

4

Neurologic Complications of Congenital Heart Disease and Cardiac Surgery in Children

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COMPLEX CONGENITAL HEART DISEASE
- Delayed Brain Development
- Co-existing Genetic Disorders and Brain Malformations
- “Silent” Brain Injury in the Neonate
- Acute Cerebrovascular Complications
- Arterial Ischemic Stroke
- Hemorrhagic Stroke
- Cerebral Venous Sinus Thrombosis
- Septic Embolism

NEUROLOGIC MANIFESTATIONS OF BRAIN DYSFUNCTION
- Acute-Onset Movement Disorders
- Acute Symptomatic Seizures
- Epilepsy
- Neurodevelopmental Disability

Congenital heart disease (CHD) is the most common major congenital malformation, occurring in approximately 1 percent of live births worldwide. Among the 40,000 children born with CHD annually in the United States, one-quarter require surgical intervention in the first year of life. With advances in surgical technique and perioperative care, survival has dramatically improved for even the most complex cardiac defects, and currently, greater than 90 percent of children with severe CHD requiring early cardiac surgery are expected to live to adulthood. Despite these successes, the neurodevelopmental sequelae of complex CHD and its treatment have increasingly emerged. Children with CHD are at risk for a myriad of neurologic complications ranging from delayed brain development in utero to arterial ischemic stroke (AIS) in childhood and adulthood, often resulting in lasting neurodevelopmental disabilities. This chapter provides a review of important neurologic abnormalities seen in the context of CHD and its treatment.

COMPLEX CONGENITAL HEART DISEASE

Complex CHD is often defined as cyanotic heart defects or CHD requiring a neonatal operation (i.e., within the first 30 days of life). Children with complex CHD are at higher risk for neurologic complications, although all individuals with CHD, regardless of complexity, are at some risk. There is significant variability in the surgical management (corrective vs. palliative) and expected anatomic outcomes of each cardiac lesion. For example, children with hypoplastic left heart syndrome (HLHS) undergo single ventricle palliation, which requires a series of palliative surgical procedures typically culminating in a Fontan procedure, allowing passive flow of systemic venous return directly to the lungs while the single ventricle provides oxygenated blood to the body. Individuals with HLHS never achieve normal circulation, and despite these multiple operations, have prolonged periods of cyanosis. In contrast, neonates with transposition of the great arteries (TGA) or other biventricular defects undergo corrective operations (e.g., arterial switch operation for TGA patients), eventually restoring normal cardiac physiology. Even these children who achieve normal cardiac physiology after corrective neonatal surgery remain at risk of varying degrees of neurodevelopmental impairments. Because HLHS and TGA account for the majority of complex CHD, much of our understanding of the impact of complex CHD

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on the brain and neurodevelopment is based on studies of children with these lesions.

Delayed Brain Development

Quantitative and qualitative magnetic resonance imaging (MRI) studies demonstrate that brain development is delayed in the context of CHD beginning in fetal life and persisting into childhood. Fetal brain MRI shows progressive impairment of brain volume during the third trimester in fetuses with complex CHD, particularly those with left-sided obstructive cardiac lesions.[1] In addition, fetuses with CHD have significant delays in brain metabolism, specifically the normal increase of brain *N*-acetyl-aspartate to choline ratios measured by magnetic resonance spectroscopy (MRS); these delays have been shown to be most prominent in fetuses with no antegrade flow in the aortic arch. Brain maturation is delayed by approximately 4 to 6 weeks in full-term newborns with complex CHD such as HLHS or TGA when compared to normal term infants in studies using brain MRI with diffusion-weighted imaging (DWI) and spectroscopy.[2] Morphometry studies have revealed lower total and regional brain volumes in newborns as well as adolescents with CHD compared to controls.

Aberrant cardiac physiology and abnormal blood flow in children with complex CHD is thought to result in delayed brain maturation beginning in the fetal period. Human cardiac development is largely completed by gestational week seven, while human brain development extends over a much longer period of time. In utero brain growth, myelination, and development of neuronal networks are dependent upon nutrients and oxygen pumped by the heart. To support rapid fetal brain maturation, blood flow to the brain increases throughout fetal life. By the third trimester, the brain is estimated to receive one-quarter of the total ventricular output, demonstrating the critical relationship between the heart and the brain. In the normal fetus, oxygenated blood from the placenta flows through the ductus venosus and preferentially streams across the foramen ovale to the left atrium and ventricle, providing highly oxygenated blood to the brain. In fetuses with TGA, the aorta and pulmonary artery are transposed and the highly oxygenated blood flows preferentially to the pulmonary vasculature rather than the cerebral vasculature. Similarly, in HLHS, inadequate left heart structures lead to reversal of blood flow through the foramen ovale with mixing of oxygenated and deoxygenated blood in the right ventricle and, in cases of aortic atresia, retrograde flow in the ascending aorta. This abnormal physiology results in decreased nutrient and oxygen delivery to the brain during critical fetal development.

Combined brain and cardiac MRI to measure fetal blood flow and oxygen saturation can be used to study the relationship between fetal hemodynamics and brain maturation. Fetuses with complex CHD demonstrate significantly lower cerebral oxygenation consumption and reduced brain volume compared with fetuses without CHD, supporting a link between brain hypoxia and impaired brain maturation. A previous investigation found that delayed surgery beyond 2 weeks of age in infants with TGA is associated with impaired brain growth on MRI and slower language development at 18 months of age compared to surgery before 2 weeks of age.[3] Prolonged periods of cyanosis and pulmonary overcirculation in children without early surgical repair may have adverse effects on brain growth and subsequent neurodevelopment.

Co-existing Genetic Disorders and Brain Malformations

Most congenital heart defects are thought to have a genetic basis, and the presence of a genetic condition is an independent risk factor for adverse neurodevelopmental outcome. Currently however, a genetic etiology is identified in only one-third of children with CHD. A few well-described chromosomal disorders (e.g., trisomies 21, 18, and 13), microdeletions (e.g., 22q11), and specific mutations (e.g., Noonan syndrome) account for a minority of patients with CHD and are associated with cognitive impairment. Nonsyndromic genetic abnormalities have also been associated with neurodevelopmental outcome. For example, in infants with complex CHD, the Apolipoprotein E ε2 allele is associated with worse early neurodevelopmental outcome, particularly motor development, independent of patient and operative factors. Currently unknown genetic and epigenetic factors may play an important additional role, as identified patient risk factors account for only about 30 percent of the expected variation in neurodevelopmental outcomes in children with CHD. In a recent study, pathogenic copy number variants were identified in greater than 10 percent of children with single ventricle lesions, only a minority of whom were noted to be dysmorphic on examination by a clinical geneticist. Genetic testing is now considered a part of standard care for all children with complex CHD.

In addition to delayed maturation, many children with CHD have structural brain malformations that may affect neurodevelopment. The prevalence of brain dysgenesis in children with CHD approaches 30 percent in some fetal MRI and autopsy studies, and varies according to the severity of CHD and the specific underlying cardiac lesion. Infants with HLHS may be at particular risk of developmental brain lesions including microcephaly, focal cortical dysplasia, agenesis of the corpus callosum, and holoprosencephaly. Brain and cardiac anomalies may occur together as a result of genetic and environmental factors, although in many children the specific genes or combination of genes that influence early anomalous development are not identified.

"Silent" Brain Injury in the Neonate

Neonates with complex CHD are at risk for acquired brain injury both pre- and postoperatively. The most common brain injuries observed in newborns with CHD are focal white matter injury (WMI) and small focal infarcts (defined as <1/3 of the arterial distribution), which are often missed by screening cranial ultrasound and more reliably detected with conventional MRI (Fig. 4-1). This type of brain injury typically occurs in the absence of neurologic signs and symptoms (i.e., "clinically silent"). Several large prospective studies using pre- and postoperative brain MRI to identify acquired brain injury in newborns with CHD have shown that up to 60 percent demonstrate evidence

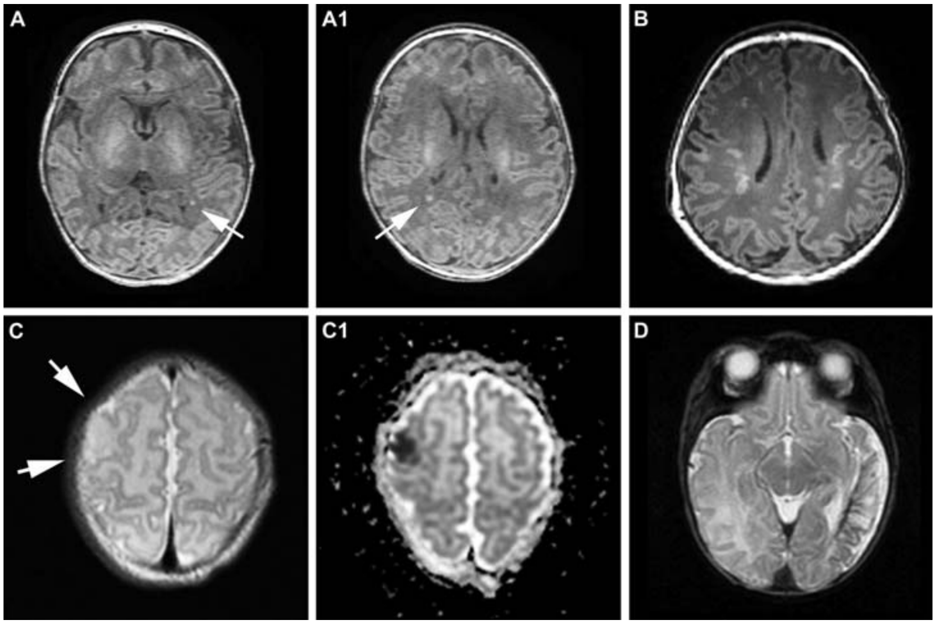

FIGURE 4-1 ■ Brain magnetic resonance imaging examples of subjects with varying degrees of white matter injury or stroke. *A, A1,* Preoperative T1-weighted images from a subject with hypoplastic left heart syndrome and moderate white matter injury (>3 foci or any foci >2 mm). There are at least two (*arrows*) small foci of hyperintensities consistent with white matter injury. *B,* Preoperative T1-weighed image from a subject with hypoplastic left heart syndrome and severe white matter injury (>5% of white matter volume). *C,* T2-weighed image from a preoperative scan on a subject with d-transposition of the great arteries. Arrows demonstrate a small focal stroke manifest as hyperintense cortical signal in the middle cerebral artery. *C1,* The corresponding average diffusivity map demonstrates reduced water diffusivity (*dark spot*) in the same region. *D,* T2-weighted image from a postoperative scan on a subject with d-transposition of the great arteries with a large subacute/chronic stroke in the middle cerebral artery distribution. (Adapted from Peyvandi S, Chau V, Guo T, et al: Neonatal brain injury and timing of neurodevelopmental assessment in patients with congenital heart disease. J Am Coll Cardiol 71:1986, 2018.[6])

of injury. Those with cyanotic heart disease are at the greatest risk.

WMI in term neonates with CHD is characterized by punctate periventricular lesions associated with T1 hyperintensity with or without DWI lesions suggesting acute injury. This pattern of injury is similar to that seen in premature infants termed "periventricular leukomalacia." The mechanism of brain injury in premature infants is thought to be due mainly to brain immaturity; oligodendrocytes during the third trimester are selectively vulnerable to hypoxia-ischemia, and therefore premature infants have a white matter-predominant pattern of injury. This mechanism of injury likely plays a key role in neonates with CHD who have preoperative brain injury. Qualitative MRI measurements of maturity have suggested that brain immaturity is a risk factor for both pre- and postoperative brain injury. Quantitative MRI techniques (e.g., diffusion tensor imaging and MRS), however, have demonstrated an association between brain immaturity and the risk of preoperative, but not postoperative, brain injury.[4] Given that WMI impacts neurodevelopmental outcomes, there remains a need for in utero strategies to improve brain development.

Estimates of the prevalence of preoperative brain injury in neonates with CHD requiring surgery range from 25 to 50 percent. Reported risk factors for preoperative brain injury include hypoxemia and time to surgery, preoperative base deficit, cardiac arrest, male sex, and the presence of aortic atresia (e.g., lack of antegrade flow in the aorta). Balloon atrial septostomy in neonates with TGA has been associated with preoperative AIS in some studies. Worse severity of preoperative injury has been shown to be significantly associated with higher neonatal illness severity scores, lower preoperative oxygen saturation, hypotension, and septostomy.[4] The clinically "silent" brain injuries identified preoperatively in neonates with CHD have a low risk of progression with surgery and cardiopulmonary bypass, and in most cases should not delay clinically necessary cardiac surgery, though expert multidisciplinary discussion is required for each case.[5]

New postoperative WMI is common, and several intra- and postoperative risk factors have been identified. Some, but not all, studies have identified circulatory arrest as a risk factor for new postoperative WMI on MRI. Other reported intraoperative risk factors include the method of blood pH management (alpha stat versus pH stat), hematocrit level, and maintaining regional cerebral perfusion during aortic arch reconstruction. In the postoperative period, overall hemodynamic stability plays an important role in mitigating the risk of new brain injury. Hypotension and hypoxemia related to low cardiac output syndrome increase the risk of brain injury. Patients with single ventricle heart disease in particular carry a higher risk of postoperative hemodynamic instability, correlating with higher risks for both postoperative brain injury as well as overall morbidity and mortality.

The "clinically silent" descriptor is misleading because these brain injuries influence later neurodevelopmental outcomes. A recent prospective longitudinal cohort study enrolled full-term newborns with single ventricle physiology or TGA, obtained pre- and postoperative MRI, and then conducted neurodevelopmental testing at 12 and 30 months of age.[6] Children with moderate to severe WMI in the neonatal period were found to have significant motor impairments at 30 months of age. However, no association was seen between small focal infarcts and outcome. Others have found that moderate-to-severe WMI is associated with reduced short-term cognitive scores and lower full-scale IQ during early childhood compared to the scores of those who have no or mild WMI.

Acute Cerebrovascular Complications

Children with cardiac disease often have disruptions in the balance of hemostasis, which may result in thrombosis, bleeding, or both. Timely and accurate diagnosis of these conditions have significant acute and longer-term management implications. Two American Heart Association/American Stroke Association (AHA/ASA) scientific statements provide a detailed review of the diagnostic evaluation and treatment of stroke in infants and children and identify important knowledge gaps in the field.[7,8]

Arterial Ischemic Stroke

Up to one-third of AISs in children results from cardiac disease. Children with CHD have a nearly 20-fold increased risk of AIS compared to the general population, and a history of cardiac surgery increases stroke risk more than 30-fold. The estimated incidence of AIS in children with cardiac disease is over 130 per 100,000 children per year, comprised primarily of children with CHD and only a small number who have acquired cardiac disease. The incidence of AIS in patients with single ventricle CHD is higher compared to those with other cardiac diagnoses (over 1,300 per 100,000 children per year). In most of these cases, the underlying cardiac disease has already been identified at the time of the stroke. While the majority of childhood strokes related to CHD occur in those who have complex congenital heart lesions with right-to-left shunting and cyanosis, stroke has been described in association with essentially all types of CHD (Table 4-1). Recent data in adults show increased risk of arrhythmia and stroke in the setting of a history of a congenital atrial septal defect. The clinical significance of patent foramen ovale in childhood stroke is currently uncertain and is an area that requires further study.

Children with complex CHD are at particularly increased risk of AIS during the neonatal period, but this increased risk extends throughout childhood and into adulthood. About one-quarter to one-half of symptomatic AIS in children with complex CHD occurs during the first month of life. Detection of acute focal neurologic injury among neonates with CHD is challenging as neurologic deficits are often subtle. New-onset seizure is the most frequent clinical manifestation of acute neonatal AIS. In older children with CHD who present with a stroke, hemiparesis is seen in up to three-quarters and seizures in up to half.

Children with AIS in the setting of CHD have significant neurologic morbidity following stroke. About three-quarters will have persistent focal neurologic deficits, and 20 percent go on to develop epilepsy. Mortality after stroke may be higher in children with CHD compared to children with stroke and no CHD, likely reflecting the severity of underlying cardiac disease. In a study of children with CHD at the Toronto site of the Canadian Pediatric Ischemic Stroke Registry, the case fatality rate was 15 percent at a median of 2 months following initial stroke, and another 16 percent died within 10 days of stroke recurrence.[9]

TABLE 4-1 ■ Congenital Heart Defects Reported with Pediatric Ischemic Stroke

Transposition of the great vessels
Hypoplastic left ventricle
Ventricular septal defect
Atrial septal defect
Tetralogy of Fallot
Pulmonary stenosis
Pulmonary atresia
Coarctation of the aorta
Eisenmenger complex
Truncus arteriosus with decreased flow
Endocardial cushion defect
Ebstein anomaly
Congenital valvular abnormalities
Patent foramen ovale (PFO) with paradoxical embolism

Data on recurrence risk following initial stroke in children and adults with CHD are scant, though one large stroke registry-based study reported a 27 percent recurrence risk at 10 years of age in children with CHD.[9] About 50 percent of these children were taking antithrombotic therapy at the time of stroke recurrence. Recurrence risk in children with CHD is equally elevated following neonatal stroke and stroke that occurs later in childhood. The risk of recurrence is highest in the period immediately following the sentinel stroke and decreases over time. Predictors of recurrent stroke include the presence of a mechanical valve, a prothrombotic condition, and an acute infection at the time of sentinel stroke. Children with non-procedure-related sentinel stroke are at greatest risk of recurrence.

All three key elements of thrombus formation—alterations in blood flow, blood composition, and vessel wall integrity—are potentially active in children with CHD. Alterations in blood flow may arise from abnormal cardiac anatomy and function or from intraluminal lines and catheters. Blood composition abnormalities including alterations in a variety of hemostatic proteins contribute to a predisposition to thrombosis. Genetic and acquired thrombophilias (due to treatment of CHD) appear to be more common in children with cardiac disease than in the general population, particularly in children with cyanotic CHD. In cyanotic CHD, endothelial injury occurs as a result of hypoxia-induced neutrophil activation, with subsequent activation of platelets and coagulation. Vessel wall integrity is further altered by central lines, cardiopulmonary bypass, or both.

Periprocedural periods are a particularly high-risk time for thromboembolic stroke. Studies report that one-quarter to two-thirds of acute AIS in children with CHD occurs around the time of procedures, with around two-thirds occurring in the post-surgical period and one-third post-catheterization. Periprocedural strokes are most common in patients with cyanotic CHD undergoing palliative surgery with a residual right to left shunt postoperatively. Other groups of children with cardiac disease who have been found to be at particularly high risk of stroke include children with a Berlin Heart EXCOR ventricular assist device (21% for ischemic stroke, 28–34% for combined ischemic and hemorrhage stroke), children treated with ECMO (7–11% for combined ischemic and hemorrhagic stroke), and children treated with the Fontan procedure (1.4–19% with various definitions of stroke).[8] While the perioperative period is a time of increased risk, about 30 percent of strokes in children with CHD occur years after palliative or corrective surgery is completed.[10] As the majority of children with CHD now survive into adulthood, recent large studies report up to a 12-fold increased risk of AIS in young adults with CHD compared to the general population. In adults with cyanotic CHD, nearly half have MRI evidence of a prior infarct.

In children with CHD, the mechanism of AIS is usually thromboembolic, specifically either cardioembolic (e.g., an intracardiac embolic source, including mural or heart valve thrombus), paradoxical (e.g., a cardiac lesion that permits an embolus of systemic venous origin access to the cerebral circulation), or from an arterial source. Infective endocarditis is a potential source of septic embolism, particularly in children with complex CHD. An intracardiac thrombus can be identified in up to 16 percent of children with cardiac disease. Cardiopulmonary bypass generates particulate or gaseous material which is not filtered by the pulmonary bed and gains direct entry into the systemic arterial circulation.

Neuroimaging for stroke in children with CHD often shows a cardioembolic stroke pattern with involvement of multiple vascular distributions. These lesions have a relatively high rate of hemorrhagic conversion likely related to the underlying embolic mechanism or the greater prevalence of anticoagulation therapy at the time of stroke. Often there is no clear source of emboli found after thorough investigation.

Cerebral or cervical vascular abnormalities may contribute further to stroke risk in children with heart disease. Up to 25 percent of children with stroke and CHD will demonstrate abnormal vascular imaging, including arterial tortuosity, developmental variants, and rarely moyamoya syndrome. Several well described disorders can be associated with both heart disease and cerebral vasculopathy including trisomy 21, Williams syndrome, neurofibromatosis type I, PHACE syndrome (posterior fossa brain malformations, hemangiomas, arterial abnormalities, cardiac anomalies, eye abnormalities), Alagille syndrome, and Noonan syndrome.

Diagnostic evaluation and treatment should follow current expert recommendations. When AIS is suspected, emergent neuroimaging is warranted if a child is a candidate for thrombolysis or thrombectomy. Typically, MRI with DWI and MRA is the preferred method of childhood AIS diagnosis due to the frequency of stroke mimics in children. When MRI is contraindicated in a child with cardiac hardware or is too difficult to obtain due to critical illness, noncontrast head CT with CT angiography and perfusion is preferred. In infants with an open fontanelle, bedside cranial ultrasound is often used to screen for large ischemic or hemorrhagic stroke, but this technique will miss smaller ischemic stroke in over half of cases.

Emergent thrombolysis and mechanical thrombectomy may be considered for older children with ischemic stroke and large-vessel occlusion at stroke centers who meet adult criteria for hyperacute treatment. These therapies have not been studied extensively in children, and potential benefits and risks need to be weighed carefully in each case. The 2019 AHA/ASA scientific statement for management of stroke in neonates and children recommends limiting consideration of hyperacute therapy to children with disabling neurologic deficits and radiographically confirmed cerebral large-artery occlusion.[8] Treatment decisions should be made in conjunction with neurologists with expertise in the treatment of children with stroke. Interventional procedures should be performed by an endovascular surgeon with experience in both treating children and performing thrombectomy in adult stroke patients. Size-based limitations for smaller arteries, contrast dye exposure, and radiation dose should be carefully considered. Centers that elect to offer hyperacute therapies should have pre-established institutional pediatric hyperacute stroke pathways.

Standard of care for management of acute AIS includes supportive neuroprotective measures including optimization of oxygenation, avoidance of hypotension, normalization of serum glucose levels, and prevention of fever. Seizures should be controlled, with a low threshold for placing an electroencephalogram to guide treatment. Initial and maintenance antithrombotic treatment for secondary stroke prevention should be considered. Transthoracic echocardiogram with bubble study should be performed to evaluate for intracardiac thrombi, infective vegetations, and risk factors for thrombi (e.g., ventricular dysfunction, right-to-left shunt). Neck imaging should be considered if no immediate cause is determined. A thrombophilia evaluation should also be considered in consultation with a hematologist.

Hemorrhagic Stroke

Few studies have examined primary hemorrhagic stroke in children with CHD, but available data suggest that the risk of hemorrhagic stroke is 13 times higher in children with CHD compared to the general population.[10] In addition to the bleeding risk associated with exposure to anticoagulation therapy, hemorrhage occurs in children with CHD as a result of decreased levels of coagulation proteins, increased fibrinolysis, or decreased platelet number or function. Cyanotic CHD can result in polycythemia, hyperviscosity, thrombocytopenia, platelet function abnormalities, disseminated intravascular coagulation, and abnormal fibrinolysis; each of these may increase the likelihood of systemic or intracranial hemorrhage.

Outcome studies of children with CHD and hemorrhage often have limited generalizability due to the high variability of underlying cardiac disease. However, acute intracranial hemorrhage can be life-threatening, and several studies indicate that hemorrhagic stroke likely worsens overall morbidity and mortality. Isolated parenchymal hemorrhage is associated with greater odds of in-hospital mortality. Hemosiderin staining on brain MRI, suggesting previous brain hemorrhage, without radiologic evidence of ischemic brain injury has been associated with worse neurodevelopmental outcomes. When intracranial hemorrhage is suspected, prompt imaging to identify the source and severity of bleeding is warranted, with rapid decision-making to stabilize the patient, balance risk and benefit of continued antithrombotic treatment to reduce the risk of rebleeding, and treat the hemorrhage. Further research focusing on hemorrhagic stroke in children with CHD is needed with special consideration of risk, benefit, and safety implications for antiplatelet and anticoagulant medications.

Cerebral Venous Sinus Thrombosis

Cerebral venous sinus thrombosis (CVST) can occur in children with CHD preoperatively or postoperatively. Often, multiple sinuses are involved, with associated ischemic or hemorrhagic intraparenchymal brain injury. Possible risk factors for CVST in children with CHD include infection, dehydration, anemia, thrombophilia, lower weight, prolonged use of a central venous catheter, or a catheter placed in the jugular vein. CVST with associated brain injury can result in significant neurologic morbidity. Diagnostic investigation for suspected CVST should include brain MRI with MR venography to evaluate for clots within the venous sinuses as well as for parenchymal injury. Specific diagnostic evaluation and treatment for CVST in general is reviewed in AHA/ASA Scientific Statements.[7,8] Supportive measures include correction of dehydration, treatment of underlying infection, control of seizures if they occur, and evaluation for signs of increased intracranial pressure. Repeat imaging at 5 to 7 days should be considered to evaluate for sinus recanalization or thrombus propagation. Older children with CVST are typically managed with anticoagulation, but for neonates with CVST there is considerable practice variation in the approach to anticoagulation, particularly in the presence of intracranial hemorrhage. Among experts who favor anticoagulation for treatment of CVST, opinion is mixed, with some support for immediate initiation of anticoagulation and others who recommend anticoagulation only after evidence of thrombus extension on serial imaging or clinical deterioration.

Septic Embolism

Infective endocarditis with secondary embolism occurs in various forms of CHD, particularly in children with cyanotic CHD, prior palliative shunt procedures, complex intracardiac repair, prosthetic valves, indwelling central venous catheters, and extensive hospitalizations with frequent use of broad-spectrum antibiotics. A prolonged course of appropriate antibiotics is the mainstay of treatment, but children with a history of prior cardiac surgery may meet indications for surgical management. Even with appropriate antibiotics, neurologic complications occur in about one-third of children with infective endocarditis involving the left side of the heart. Larger vegetations or infection with high-risk organisms are associated with an increased risk for cerebral embolization and may be an indication for early surgical intervention. Infarction can occur in any vascular distribution, but the anterior circulation is most common. Brain abscesses, meningitis, vasculitis, and hemorrhage from mycotic aneurysms are also potential complications. The risk of cerebral hemorrhage from mycotic aneurysms or large ischemic infarcts is often considered a contraindication for anticoagulation, but in the presence of a mechanical valve, the risk versus benefit of anticoagulation must be weighed carefully. If anticoagulation for a mechanical valve is temporarily interrupted because of infective endocarditis, timing of reintroduction of anticoagulation should be considered carefully.

NEUROLOGIC MANIFESTATIONS OF BRAIN DYSFUNCTION

Acute-Onset Movement Disorders

Choreoathetosis was once a common neurologic complication following cardiac surgery in children, but the incidence has decreased substantially with modifications in perioperative management. Nevertheless, in the first week after surgery some children will develop a movement disorder characterized by hyperkinetic movements involving the face and extremities. When they occur, these movement disorders tend to be refractory to a wide range of drugs, and often are only controlled by sedating medications. Some mild forms resolve, but severe forms can persist long term. Brain MRI rarely reveals a focal lesion and more often shows diffuse cerebral atrophy without typical features of infarction. Classes of medications used for treatment of these movement disorders are similar in this population as in others. In addition, agitation and insomnia can frequently develop, and treatment should include strategies to address these complications.

Acute Symptomatic Seizures

Children undergoing cardiac surgery for repair of complex CHD are at risk for acute symptomatic seizures in the early postoperative period, and these events often signal newly acquired brain injury. Several large cohorts of neonates and infants undergoing continuous EEG monitoring (cEEG) following cardiac surgery have demonstrated seizures in about 10 percent of patients, with the majority occurring without any clinical manifestation and only identified on EEG. Seizure onset typically occurs within the first few days postoperatively, most often between 12 and 36 hours. The seizure burden is often high, with status epilepticus occurring in greater than 50 percent of patients with seizures.

The American Clinical Neurophysiology Society's 2011 guideline on neonatal EEG monitoring recommends consideration of cEEG following neonatal cardiac surgery. Using this guideline, a 2015 single-center study reported an electrographic seizure incidence of 8 percent among neonates with CHD who received cEEG following surgery with cardiopulmonary bypass; 85 percent of these seizures were not detected clinically.[11] In this study, bedside providers indicated clinical concern for abnormal movements and vital sign instability in numerous patients that were nonepileptic on EEG, highlighting the difficulty of accurately diagnosing seizures without EEG in young patients.

Risk factors for seizures have been reported in various CHD cohorts and include co-existing genetic defects, increasing duration of circulatory arrest, delayed sternal closure, and aortic arch obstruction. Seizures are also more likely in neonates who suffer cardiac arrest or require extracorporeal membrane oxygenation (ECMO) postoperatively. Overall, neonates with seizures may have higher illness severity than those without seizures. Among neonates who were monitored by cEEG after surgery with cardiopulmonary bypass, neonates with seizures had a significantly higher mortality than neonates without seizures.[11]

Newly acquired brain injury is the most important concern when new-onset seizures occur in a child with CHD. Numerous studies have shown that most children with postoperative EEG-confirmed seizures have a variety of imaging abnormalities including hypoxic-ischemic injury, WMI, focal or multifocal ischemic infarcts, or intracranial hemorrhage. However, seizures in children with CHD may also be related to acute metabolic abnormalities such as hypoglycemia, hypocalcemia, fever, infection, or an underlying predisposition to seizures in children with cerebral dysgenesis. Delayed brain maturation seen in children with CHD may also play a role by increasing excitatory mechanisms that predispose them to seizures. Postoperative seizures in children with complex CHD are associated with worse neurodevelopment outcomes, in part because they often indicate an acquired brain injury or underlying genetic syndrome. In the Boston Circulatory Arrest Study, which measured neurodevelopmental outcomes of children with TGA following arterial switch surgery, the presence of a postoperative seizure was the medical factor most consistently associated with worse neurodevelopmental outcome at 16-year follow up.[12]

Seizures should be treated promptly when they occur. The choice of antiseizure medication is not unique for this population, although the hemodynamic status of these patients can sometimes pose particular challenges. Avoidance of medication-related hemodynamic instability is important. Acute seizures are often difficult to treat, particularly in cases of status epilepticus, frequently requiring multiple antiseizure medications to achieve control. Postoperative seizures should prompt neuroimaging after seizures are controlled and hemodynamic changes are stabilized.

Epilepsy

The prevalence of epilepsy in children and adults with CHD is higher than in the general population. Children who have acute symptomatic seizures after cardiac surgery in particular have a high frequency of developing epilepsy. In a case-control study of 15,222 children born and diagnosed with CHD between 1980 and 2010, the overall cumulative incidence of epilepsy in children with CHD was 5 percent by 15 years of age, excluding epilepsy diagnoses made 7 days before and 30 days after surgery.[13] In the subgroup of children with CHD who were born at term without extracardiac anomalies or genetic syndromes, the cumulative epilepsy incidence was 3 percent by 15 years of age. Overall, people with CHD were nearly four times as likely to develop epilepsy compared with the general population before 5 years of age, and over twice as likely from 5 to 32 years of age. The risk of epilepsy was highest in those who underwent multiple surgeries, but remained elevated compared to the general population even in those who received no surgical intervention and who had no history of prematurity or extracardiac defects.

Neurodevelopmental Disability

As survival of children with complex CHD has improved, neurodevelopmental disability has emerged as the most common comorbid outcome. Overall, children with complex CHD who survive surgery in infancy have more problems with learning, reasoning, executive function, attention and impulse control, language, and social behavior compared with children without CHD. While outcomes can vary significantly by cardiac lesion, the unique developmental profile of children with CHD has been termed the “neurodevelopmental signature of complex CHD.” Although children without genetic syndromes or severe neurologic events have near normal intelligence, some have pervasive, but often subtle, cognitive and behavioral problems. The developmental profile of these children changes in each stage of life, and early testing may underestimate ultimate functional impairments. To address this health concern, guidelines have been created for performing serial neurodevelopmental assessments of at-risk children with CHD.[14] In addition to having a high-risk cardiac lesion, the guidelines recommend serial screening for patients with CHD in combination with: prematurity (<37 weeks), developmental delay recognized in infancy, suspected genetic anomaly, history of ECMO, heart transplantation, a history of cardiopulmonary resuscitation, prolonged perioperative hospitalization, perioperative seizures, and abnormal neuroimaging. Early detection of impairments and appropriate intervention services are important to optimize functional outcome.

Neurodevelopmental outcomes related to CHD have been studied in most detail in children with TGA and single ventricle CHD. The Boston Circulatory Arrest Study was a randomized trial comparing the neurodevelopmental outcomes of children with TGA who underwent the arterial switch operation using deep hypothermia with either total circulatory arrest or continuous low-flow bypass as the main method of vital organ support.[12] This cohort was followed for both short- and long-term neurodevelopmental outcomes at 1, 4, 8, and 16 years. At 16 years of age, both groups continued to exhibit deficits in academic achievement, memory, executive function, visuospatial skills, attention, and social cognition compared to expected population means. The majority of these adolescents had a history of frequent use of special services (65%) including tutoring (37%), grade retention (17%), special education (25%), and psychotherapy or counseling (25%). In addition, 12 percent were taking at least one medication for a psychiatric disorder (often attention deficit hyperactivity disorder, ADHD), representing a fourfold increased rate compared to the reference group. More recently, these investigators found that deficits in attention at 8 years of age strongly predicted worse psychosocial health status at 16 years of age, and therefore, early detection and treatment of ADHD may have a meaningful impact on long-term psychologic well-being in this population. Patients with single ventricle heart disease, particularly those with HLHS, are known to have the highest degree of neurodevelopmental impairment, particularly when it comes to motor outcomes. Several studies have noted that children with HLHS also tend to have lower IQs and problems with visuospatial skills, expressive language, attention, and externalizing behavior.

Risk factors for adverse neurodevelopmental outcomes are multifactorial and cumulative over time. Neurologic and developmental impairments may be influenced by multiple contributing factors including co-existing genetic disorders, congenital brain anomalies, nongenetic patient factors, type of cardiac lesion (particularly those with abnormal fetal cerebral oxygenation and postnatal cyanosis), perioperative factors associated with prolonged postoperative course, and acquired brain injury. Early studies of neurodevelopmental outcomes following cardiac surgery in infancy focused primarily on surgical techniques. These studies led many institutions to adjust intraoperative management strategies, particularly avoidance of deep hypothermic circulatory arrest. However, factors other than intraoperative management strategies may be more important determinants of neurodevelopmental outcomes for many children. In a 2015 study of combined participant data from all of the single-center studies of individuals with CHD undergoing cardiac surgery in infancy, cognitive and motor outcomes were more highly associated with innate patient and preoperative factors (e.g., race, gender, birth weight, genetic anomalies, type of CHD, and maternal education) and postoperative factors (e.g., use of ECMO and longer postoperative length of stay) than with specific techniques used during surgery.[15]

In adolescent survivors of neonatal cardiac surgery, white matter abnormalities and volume loss persist, and are associated with neurodevelopmental disabilities at this age. In addition, delayed brain maturation and vulnerability to white matter injury likely plays a further role. Persistent abnormal brain maturation seen on MRI in adolescent survivors of surgery with cardiopulmonary bypass who did not have other MRI abnormalities, particularly those with cyanotic heart disease, has been shown to be associated with adverse cognitive, motor, and executive function outcomes. At 16-year follow up of the Boston Circulatory Arrest Study, the strongest predictor of neurodevelopmental outcome was not a medical risk factor but rather family socioeconomic status, which accounted for the largest percentage of explained variance in outcomes.[12]

Neurocognitive function has not yet been well studied in adults with complex CHD, although limited research shows that they continue to demonstrate deficits across various domains as seen in children. During the transition years from childhood to adulthood, more than half of individuals with CHD stop accessing medical care. This may be influenced, at least in part, by neurodevelopmental disabilities including executive dysfunction. Studies are needed to determine if early neurodevelopmental evaluation and intervention, with ongoing information from medical providers about the importance of follow-up care, can help to address this problem. Additionally, ongoing research will address how cognitive and behavioral deficits may impact educational achievement, employment opportunities, relationships, and quality of life for adults with CHD.

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CHAPTER

5

Neurologic Manifestations of Acquired Cardiac Disease and Arrhythmias

RYAN T. MUIR ■ DAVID J. GLADSTONE

INTRODUCTION

CARDIOEMBOLIC STROKE

- Clinical Features
- Investigations
  - *Brain and Vascular Imaging*
  - *Echocardiography*
  - *Electrocardiographic Monitoring*

CARDIAC CAUSES OF ISCHEMIC STROKE

- Left Atrium
  - *Atrial Fibrillation and Flutter*
  - *Chronic Sinoatrial Disorder (Sick Sinus Syndrome)*
  - *Atrial Myxoma*
- Interatrial Septum: Paradoxical Embolus
- Left Ventricle
  - *Acute Myocardial Infarction*
  - *Cardiomyopathies*
  - *Left Ventricular Dysfunction*
- Valvular Diseases
  - *Mitral Annular Calcification*
  - *Mitral Valve Prolapse*
  - *Mitral Valve Regurgitation*
  - *Mitral Valve Stenosis and Rheumatic Heart Disease*
  - *Aortic Valve Stenosis*
  - *Lambl Excrescences*
  - *Prosthetic Heart Valves*
- Endocarditis
  - *Infective Endocarditis*
  - *Marantic (Nonbacterial Thrombotic) Endocarditis*

MANAGEMENT OF CARDIOGENIC BRAIN EMBOLISM

- Emergency Reperfusion Treatment
  - *Thrombolysis*
  - *Endovascular Therapy*
- Stroke Prevention
  - *Anticoagulant Therapy for Atrial Fibrillation*
  - *Treatment Decisions*
  - *Acute Myocardial Infarction*
  - *Cardiomyopathy and Left Ventricular Dysfunction*
  - *Patent Foramen Ovale*

SYNCOPE

- Clinical Manifestations
- Cardiac Etiologies
  - *Structural Heart Disease*
  - *Arrhythmias: Conduction Abnormalities*
  - *Arrhythmias: Channelopathies*

CARDIOMYOPATHIES WITH ASSOCIATED NEUROLOGIC MANIFESTATIONS

INTRODUCTION

The neurologic manifestations of acquired cardiac disease include (1) the sudden onset of a focal neurologic deficit due to occlusion of a cerebral or retinal artery by an embolus that has developed within the heart (cardiogenic embolism) and (2) transient, self-limited episodes of generalized cerebral ischemia that occur as a consequence of brief failure of cardiac output, due to rhythm disturbances or outflow obstruction, resulting in presyncope or syncope. Exceptions to these categorizations include atrial fibrillation (AF), an arrhythmia that is associated with embolus formation rather than syncope, and chronic sinoatrial disorder, which predisposes to both syncopal and embolic disturbances. This chapter reviews these neurologic manifestations, including the acute management and prevention of cardioembolic stroke, and also briefly discusses cardiomyopathies and their associated neurologic manifestations beyond stroke and syncope.

CARDIOEMBOLIC STROKE

Ischemic stroke or transient ischemic attack (TIA) results from the sudden interruption of perfusion

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to a region of neural tissue, causing an abrupt interruption of behavior that corresponds to that region's topographic function. Many ischemic strokes are embolic. While most emboli are composed of thrombus, some—depending on their etiology—may be composed of tumor cells, calcific fragments, or infective components.[1] Arterial emboli may originate from the heart chambers or valves, from the aortic arch or the large extracranial and intracranial arteries (atherosclerotic plaque or dissection), paradoxically from the venous system through a right-to-left shunt, or systemically during prothrombotic states.

Cardiogenic embolism accounts for about 20 percent of ischemic strokes.[1] Approximately 25 percent of ischemic strokes are due to large-artery atherosclerotic disease, 25 percent relate to intracranial disease of small arteries, and 25 percent are cryptogenic, having no identifiable cause. The term *embolic strokes of undetermined source* (ESUS) has been defined as follows: (1) nonlacunar ischemic stroke on computed tomography (CT) scan or magnetic resonance imaging (MRI), (2) absence of extracranial or intracranial atherosclerosis causing more than 50 percent stenosis in arteries supplying the region of ischemia, (3) no major-risk cardioembolic source of embolism identified, and (4) no other specific cause of stroke identified (arteritis, dissection, recreational drug use, migrainous infarction, or vasospasm).[1]

Cardiogenic brain embolism often manifests with greater clinical severity than strokes of other etiologies. In a population-based study of first stroke, patients with cardioembolic stroke had the lowest 2-year survival rate (55%) and were three times more likely to die than those with small-artery occlusion. The major etiologic categories of cardiogenic embolism are arrhythmias, atrial structural abnormalities, valvular heart disease, cardiomyopathies, cardiac tumors, infective and noninfective endocarditis, paradoxical emboli, and iatrogenic.

The most common cardiac cause of ischemic stroke is AF, which accounts for at least one-sixth of all strokes, and this proportion increases with increasing patient age.[1–3] In addition to persistent or paroxysmal AF, other major-risk cardiac sources of emboli include intracardiac thrombus, mechanical cardiac valve, atrial myxoma and other cardiac tumors, rheumatic valve disease, recent myocardial infarction (within 4 weeks), left ventricular ejection fraction less than 30 percent, and endocarditis. Other cardiac causes of stroke are listed in Table 5-1.

TABLE 5-1 ■ Established and Putative Cardiac Causes of Stroke

Major Etiologic Category	Subtypes
Arrhythmia	Atrial fibrillation* Atrial flutter* Atrial high-rate episodes† Atrial asystole and sick sinus syndrome†
Left atrial abnormalities	Left atrial or appendage thrombus* Spontaneous echo contrast (smoke)† Atrial myopathy† Atrial septal aneurysm† Chiari network†
Valvular heart disease	Mechanical valves* Rheumatic heart disease* Mitral valve prolapse Myxomatous valvulopathy with prolapse† Mitral annular calcification† Aortic valve calcification† Aortic valve stenosis† Lambl excresences†
Left ventricular abnormalities	Acute myocardial infarction (<4 wk)* Left ventricular systolic dysfunction (ejection fraction <30% or regional akinesis)* Left ventricular diastolic dysfunction† Left ventricular endomyocardial fibrosis†
Cardiac masses	Atrial myxoma* Papillary fibroelastoma* Cardiac thrombus* Metastasis
Endocarditis	Infective* Marantic (thrombotic, nonbacterial)*
Paradoxical embolus	Patent foramen ovale† Atrial septal defect† Pulmonary arteriovenous fistula†
Aortic arch	Complex aortic arch atheroma*
Iatrogenic	Cardiac surgery Cardiac catheterization Percutaneous coronary intervention Cardioversion for atrial fibrillation and flutter

*High-risk cardiac sources of embolism.[4]
†Minor-risk sources.[1]

Some patients with ESUS may have cardiogenic embolism as many are found to have some of the common minor-risk cardiac sources of embolism listed in Table 5-1. Long-term follow-up of patients with ESUS reveals paroxysmal AF in up to 30 percent. Emerging evidence suggests that some cryptogenic strokes may arise from an enlarged, fibrotic, and poorly contractile left atrium (i.e., “atrial myopathy”) in the absence of AF.[4] Other cardiac abnormalities found in ESUS patients include ventricular systolic or diastolic dysfunction, left ventricular wall motion abnormalities, myxomatous mitral valve, mitral annular calcification, atrial septal defects, and aortic stenosis.[1] These abnormalities are common and, in large population studies, have been associated with increased risk of stroke, but whether their presence implies causality in an individual patient with ESUS remains uncertain.

Clinical Features

Clinical features alone cannot reliably reveal the underlying type or etiology of ischemic stroke. This determination requires brain imaging, vascular imaging, and cardiac assessment by echocardiography and electrocardiography (ECG). Nonetheless, some clinical clues may be suggestive of a cardioembolic source of embolism.

Cardioembolic strokes often present with sudden neurologic deficits which are maximal at onset. This is in contrast to some cases of small-vessel occlusion where the onset of stroke deficits may begin with a gradually progressive or fluctuating course, probably reflecting fluctuations in blood pressure.

Furthermore, “cortical signs” are more common in cardioembolic stroke as emboli are more likely to lodge in distal arteries supplying the cortex. This is in contrast to occlusion of small vessels that supply the subcortical gray and white matter, sparing cortical regions. Cortical signs include forced gaze deviation, homonymous visual field deficits respecting the vertical meridian, hemispatial neglect, and aphasia of all types. Importantly, neurologic deficits that localize to multiple different vascular territories are also highly suggestive of a cardiogenic mechanism of stroke (Table 5-2).

Investigations

BRAIN AND VASCULAR IMAGING

The first diagnostic investigation for suspected acute stroke is usually a noncontrast CT scan of the brain to exclude intracranial hemorrhage.[2] Cardioembolic strokes can cause isolated cortical infarcts, combined

TABLE 5-2 ■ Clinical Features Suggestive of Cardioembolic Stroke

Clinical Entity	Descriptor
Onset/course	Sudden onset, reaching maximal deficit within 5 min of onset Nonfluctuating neurologic deficits Rapid dramatic neurologic recovery
Severity	Impaired consciousness at stroke onset* High score on NIH stroke scale
Cortical signs	Aphasia Neglect (tactile or visuospatial; localizing to parietal lobe) Homonymous visual field deficit (localizing to temporal or parietal optic radiations or occipital cortex) Forced eye deviation (localizing to frontal eye field)
Clinical localization	Neurologic deficits localize to more than one vascular territory
Systemic signs	Fever† Livedo reticularis (suggestive of Sneddon syndrome, APLA, or SLE) Evidence of systemic embolization (Janeway lesions†, Osler nodes†, septic arthritis†, Roth spots†, cellulitis†, discitis†, signs of spinal cord infarct or ischemic limb) Venous thrombosis in legs (suggestive of hypercoagulable state)
Cardiac auscultation	Murmur of mitral stenosis Murmur of mitral regurgitation†
Investigations	ECG–ST elevation myocardial infarct, atrial fibrillation, atrial flutter TTE–evidence of intracardiac thrombus, vegetations†, wall motion abnormality, aneurysm, intracardiac tumor, valvular heart disease or left atrial enlargement Neuroimaging–acute strokes in multiple vascular territories Imaging evidence of systemic embolization–renal infarct or splenic infarct†

APLA, Antiphospholipid antibody syndrome; NIH, National Institutes of Health; SLE, systemic lupus erythematosus; TTE, transthoracic echocardiography.
*Also occurs with hemorrhagic stroke.
†Suggests infective endocarditis.

cortical and subcortical infarcts, infarcts in the territory of large vessels, or showers of multiple acute small emboli. Acute embolic ischemic lesions that are bilateral or affecting different vascular territories in the same hemisphere simultaneously (e.g., anterior and posterior circulation) are highly suggestive of a cardiac source of embolism. In contrast, isolated deep subcortical infarcts smaller than 1.5 cm (lacunes) are usually due to small-vessel cerebrovascular disease rather than cardioembolism.[3] A hyperdense vessel sign on noncontrast head CT may indicate an acute thrombus. For evaluating early acute ischemic changes on head CT in patients presenting within the first hours of symptom onset, a popular rating scale is the Alberta Stroke Program Early CT score (ASPECTS). CT scans have some limitations—acute ischemic stroke may not become visible for several hours, artifact may partially obscure the posterior fossa, and ischemia in the brainstem and cerebellum can be difficult to identify.

CT angiography (CTA) and magnetic resonance angiography (MRA) are important vascular imaging tests for the diagnostic evaluation of patients with stroke or TIA. CTA can be acquired rapidly and has become the vascular imaging procedure of choice at many emergency departments for patients presenting with stroke symptoms. CTA aids patient selection for acute stroke treatments (thrombolysis, endovascular therapy) and helps guide secondary stroke prevention management. It can identify embolic occlusions, vascular stenosis, and other vasculopathies within the major intracranial and extracranial arteries. When acquiring CTA it is important to capture the arch of the aorta; the origins of the common carotid and vertebral arteries and their course to the circle of Willis; and the branches off the circle of Willis to their distal termination. CTA can visualize aortic arch atheroma that can be a source of cerebral emboli, especially if large, mobile, or ulcerated.[3] In the assessment of acute stroke, multiphase CTA permits an assessment of the integrity of the collateral vessels, and CT perfusion studies measure cerebral blood volume, blood flow, and mean transit time.[2] The ability to identify potentially salvageable brain tissue with advanced imaging such as CT perfusion has enabled extended time windows (beyond 4.5 hours) for stroke treatment to be evaluated in clinical trials. The acute occlusion of a blood vessel causes a local core of infarction surrounded by brain tissue that is ischemic but not yet infarcted (penumbra). This brain tissue may survive temporarily by recruiting blood from collateral arteries and more permanently if perfusion can be restored expeditiously. Acute treatments are discussed later in this chapter.

MRI with diffusion-weighted imaging (DWI) sequences is far superior to noncontrast CT for identifying acute ischemia and small infarcts.[2] As there are many stroke and TIA mimics (e.g., seizure, hypoglycemia, metabolic derangements, and migraine), MRI is invaluable in distinguishing between the various possibilities.[2] The pattern of DWI abnormalities can help also to determine the most likely etiology of stroke. Acute strokes in more than one vascular territory are highly suggestive of a shower of emboli from a proximal source.[2] The anterior circulation is affected four times more frequently than the posterior in cardioembolic stroke. MRI is the best modality to evaluate for ischemia acutely in the posterior circulation given the limitations of CT. On MRI, the presence of multiple acute infarcts, simultaneous infarcts in different circulations, multiple infarcts of different ages, and isolated cortical infarcts predict a greater 90-day risk of stroke recurrence.[2] CT or MRI is also important in evaluating for and predicting hemorrhagic transformation after an acute infarct. Predictors of hemorrhagic transformation include larger infarcts, greater stroke severity, treatment with tPA or anticoagulation, and older age.

ECHOCARDIOGRAPHY

Echocardiography plays an important role in the diagnostic work-up of embolic stroke. Transthoracic echocardiography (TTE) is easily administered and is noninvasive, but transesophageal echocardiography (TEE) is more sensitive and specific for detecting cardiac sources of embolism. TTE can image the left ventricle well, assess left ventricular function, identify akinetic segments, and reveal thrombus (may require contrast), prosthetic valve thrombus, endocarditis, cardiac tumors, and patent foramen ovale (PFO). TEE is better for assessing the left atrium, appendage, interatrial septum for PFO and valve vegetations. Echocardiography should be ordered judiciously; appropriate use criteria have been published.[4]

For PFO detection, the diagnostic sensitivity is about 50 to 60 percent with TTE (with saline bubble study) and 90 percent with TEE. Transcranial Doppler (TCD) ultrasound has a 96 percent sensitivity for detecting right-to-left cardiac shunts by identifying microbubbles reaching the middle cerebral artery. In cryptogenic stroke cases where PFO may be causal, lower limb venous Doppler ultrasound can evaluate for deep vein thrombosis (DVT).

ELECTROCARDIOGRAPHIC MONITORING

ECG is necessary for the diagnosis of AF. Given that AF is frequently paroxysmal and asymptomatic, it can easily be missed by a single 12-lead ECG or short-duration ECG monitoring. In patients with ischemic stroke presenting in sinus rhythm, ECG monitoring for 24 to 72 hours permits a new diagnosis of paroxysmal AF to be made in about 5 percent of patients. Randomized controlled trials have demonstrated that after an ischemic stroke, prolonged ECG monitoring with external wearable monitors (or implantable loop recorders) significantly increases the detection of AF. The longer the duration of monitoring, the greater is the probability of finding AF. The goal of such monitoring is to find a sufficient burden of AF to benefit from anticoagulant treatment. When only very brief, subclinical AF is detected, the clinical significance and treatment implications are still a matter of uncertainty and debate. In patients with pacemakers, subclinical AF is common and is associated with an increased risk of stroke. However, the stroke risk associated with brief device-detected subclinical AF appears lower than the stroke risk with clinical AF and the role of anticoagulant therapy in such cases is currently being tested in randomized trials. Reports by the AF-SCREEN International Collaboration provide a review and recommendations regarding AF screening after stroke and in the general population.[5,6]

CARDIAC CAUSES OF ISCHEMIC STROKE

Left Atrium

ATRIAL FIBRILLATION AND FLUTTER

AF is the most common serious arrhythmia and is associated with a three- to fivefold increase in the risk of stroke.[3] It is also associated with an increased risk of cognitive impairment and dementia. AF accounts for nearly half of all cardiac causes of stroke and more than one-quarter of strokes in the elderly. Strokes associated with AF tend to be more severe, more disabling, and have a higher mortality than ischemic strokes due to other causes.

The prevalence of AF in the general population is age dependent, ranging from 0.1 percent among adults younger than 55 years of age to 10 percent in those 80 years or older.[3,5] AF currently affects 33 million people worldwide. With an aging population, the prevalence of AF and of AF-associated strokes is projected to increase.[5] Atrial flutter also confers a greater risk of thromboembolism and often co-exists with AF, as they share similar pathophysiologic substrates.

Risk factors for AF include advanced age, hypertension, obesity, diabetes mellitus, underlying cardiac pathologies,[5] hyperthyroidism, heavy alcohol consumption, and a sedentary lifestyle.[5] Cardiac conditions associated with AF include valvular heart disease, rheumatic heart disease, congestive heart failure, coronary artery disease, cardiomyopathy, mitral valve prolapse, mitral annular calcification, and left atrial enlargement.[5] However, AF may also occur as "lone AF" in young patients who do not have structural cardiac disease.

AF is not a binary entity and there are varying degrees of AF burden—the amount of time spent in AF—that vary between patients and over time in individual patients. AF can be symptomatic or asymptomatic and is classified as paroxysmal (self-terminating episodes lasting less than 7 days), recurrent (two or more episodes), persistent (more than 7 days), or permanent (continuous for more than 12 months). Paroxysmal AF is the most common subtype and is associated with a lower risk of stroke and lesser stroke severity than persistent AF.

Reversible or temporary causes of AF include acute systemic illness such as sepsis or pneumonia, alcohol, surgery, hyperthyroidism, acute myocardial infarction, pulmonary embolism, and pericarditis. In these precipitated settings, AF has been termed "secondary AF" and previously was thought not to increase stroke risk. However, studies now show that those with secondary AF may have an equivalent stroke risk to those with spontaneous AF. This highlights the fact that the acute medical precipitant of secondary AF merely reveals an underlying vulnerable atrial substrate which can confer an independent risk of stroke.

In patients with atrial flutter, the risk of thromboembolism is less than that of AF, but higher than for patients in sinus rhythm. Patients with atrial flutter often develop AF and the two atrial tachyarrhythmias frequently co-exist. For practical purposes, the anticoagulant treatment recommendations for atrial flutter are the same as those for AF.

Pathophysiology

The pathogenesis of AF relates to atrial cardiopathy. Histologically, atrial cardiopathy is characterized by interstitial fibrosis, loss of sarcomeres, and accumulating glycogen granules within atrial cardiomyocytes.[5,7] This process is likely driven by a multifactorial interaction of risk factors including increasing age, genetic predisposition, dysrhythmias, local and systemic inflammation, endothelial dysfunction, and left atrial dilatation/myocardial stress (caused by systemic hypertension, pulmonary hypertension, elevated left ventricular filling pressure, heart failure, and/or mitral valve dysfunction). With increasing age, in conjunction with the aforementioned risk factors and left atrial dilatation, structural remodeling of the left atrial connective tissue occurs with the formation of atrial fibrosis.[7] Furthermore, a critical component of AF pathogenesis is that the electrical disturbance of AF begets the formation of additional aberrant left atrial fibrotic substrate that propagates further AF.

As mentioned, myocardial stress promotes left atrial dilatation and further atrial fibrotic remodeling. An established biomarker of myocardial dysfunction is N-terminal fragment B-type natriuretic peptide (NT-proBNP), which is secreted in the atrium secondary to atrial or ventricular dysfunction. Elevated NT-proBNP has been associated with an increased risk of AF and thromboembolic events.[5]

Myocardial ischemia also independently affects atrial fibrosis. In patients with AF, an elevated troponin in the blood is associated with an independent risk of stroke or systemic embolism.[5] In such cases, troponin is likely an additional marker of vulnerable myocardium indicating ischemia, volume and pressure overload, or myocardial structural abnormalities.[5] With this vulnerable myocardium, therefore, AF can be precipitated acutely during states of increased cardiac output and demand, such as pneumonia, sepsis, hyperthyroidism, and alcohol intoxication, thereby not only increasing stroke risk acutely but also promoting further aberrant left atrial remodeling.

There is emerging evidence that elevated levels of inflammatory markers, namely interleukin-6 (IL-6) and C-reactive protein (CRP), can be associated with the presence and burden of AF, and in those with AF they may identify greater risk of cardiovascular morbidity and mortality.[5] These markers could reflect a prothrombotic state in AF, may reflect an inflammatory contribution to the development of aberrant atrial substrate, or not be causal at all.

There has been a shift in thinking regarding the manner in which AF leads to cardioembolic stroke.[4] The traditional model has been that the dysrhythmia of AF leads to uncoordinated atrial function, thereby promoting left atrial stasis of blood that can lead to thrombus formation with eventual embolization to the brain. However, this century-old hypothesis incompletely captures the pathogenesis of embolic stroke in AF. The findings from trials of rate and rhythm control in paroxysmal AF have not demonstrated a reduced stroke risk and suggests that there may be another mediator of thromboembolism that is related to AF but that is not necessarily AF itself.[7] There is an emerging appreciation that an abnormal left atrial substrate (endothelial dysfunction, fibrosis, left atrial dilatation, and left atrial appendage dysfunction) may be associated with cardioembolic stroke pathogenesis independent of AF.[7] It is more likely that an aberrant left atrial substrate—atrial cardiopathy—is both sufficient to cause cardioembolic stroke and necessary for AF to arise. When AF arises, superimposed on an aberrant atrial substrate, there is an even greater risk of cardiogenic embolism. A newly proposed model of left atrial cardiopathy and AF in the pathogenesis of cardioembolic stroke is summarized in Fig. 5-1.

Risk Stratification

The average annual risk of stroke in individuals with AF is 5 percent and is heavily dependent on age and the presence of additional risk factors. The most important predictor of stroke risk in patients with AF is a history of thromboembolism (i.e., previous TIA, stroke, or systemic arterial embolism). Other independent risk factors for stroke in patients with AF are increasing age, hypertension, congestive heart failure, diabetes mellitus, female sex, systolic hypertension, and left ventricular dysfunction.

There are two commonly used clinical tools to predict the risk of stroke in patients with AF based on the presence of additional risk factors. These are the CHADS_2 score (*C*ongestive heart failure,

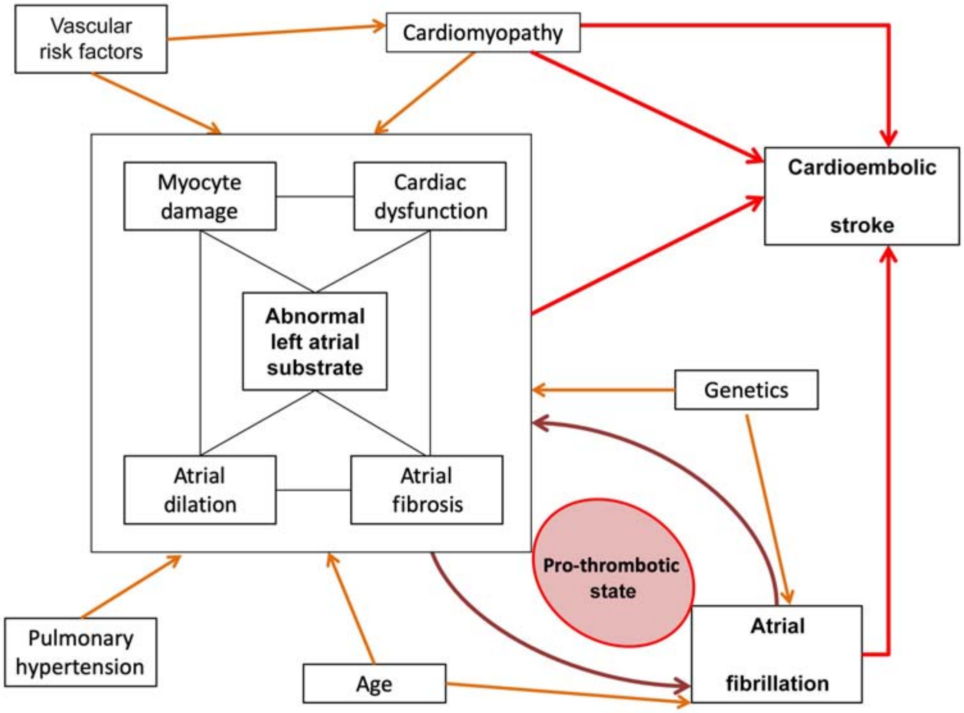

FIGURE 5-1 ■ Model of left atrial myopathy and atrial fibrillation as mechanisms of cardioembolic stroke.

*H*ypertension, *A*ge ≥75 years of age, *D*iabetes, *S*troke or TIA) and the CHA$_2$DS$_2$-VASc scale, which adds on points for *V*ascular disease (coronary artery disease or peripheral vascular disease), *A*ge ≥65 years of age or ≥75 years of age, and female *S*ex. The CHADS$_2$ scale ranges from 0 (low stroke risk, 1.9% per year) to 6 points (high stroke risk, 18.2% per year). The CHA$_2$DS$_2$-VASc scale is particularly helpful in discerning risk in those who score 0 or 1 on CHADS$_2$, and helps guide treatment decisions in these cases.

Another clinical risk factor associated with AF and independently associated with ischemic stroke is obstructive sleep apnea. During sleep, apneic episodes induce hypoxemia and sympathetic stimulation, which can induce tachycardia and nocturnal surges of hypertension, all of which can exacerbate AF.[7]

There is interest in exploring biomarkers to help improve stroke risk prediction beyond the clinical CHADS scores. The duration and burden of AF are also important contributors to stroke risk in AF. There is a greater risk of stroke in those with persistent and permanent AF compared to paroxysmal AF. Despite this, current guidelines regarding treatment decisions have not incorporated AF burden in the determination of stroke risk in AF. Furthermore, non-AF arrhythmias may be suggestive of an abnormal atrial substrate. Frequent atrial ectopy (premature atrial beats) is associated with AF. Both frequent atrial ectopy and paroxysmal supraventricular tachycardia are associated with stroke risk independent of AF.[7]

Echocardiographic features have been used for risk stratification in patients with AF. Left atrial enlargement, especially a diameter exceeding 45 mm or a left atrial volume index of 32 mL/m^2 or more can potentiate a greater risk of stroke and systemic embolism.[7] These markers are probably indicators of stasis and endothelial dysfunction.[7] Furthermore, the left atrial appendage (LAA) is a common and known source of emboli in patients with AF as it is a low-pressure and highly trabeculated sac vulnerable to thrombus formation (Fig. 5-2).[7] The presence of LAA thrombus, best visualized with TEE, predicts an increased risk of stroke. LAA function can also be assessed on TEE and is emerging as a biomarker of stroke risk in AF. LAA flow velocity is reduced in AF and a velocity of <0.2 m/sec or spontaneous echo contrast on TEE is associated with an increased risk of thrombus formation and embolic events in AF.[7] Spontaneous echo contrast or a “smoke-like” appearance on TEE represents stasis of blood in the atrium, and its presence may be a marker of increased stroke risk. There are also associations between stroke risk and LAA

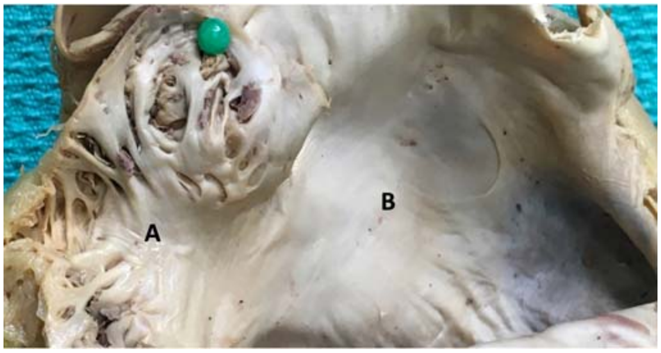

FIGURE 5-2 ■ Gross anatomic view of *A*, left atrial appendage (LAA) and *B*, left atrium (LA). The high density of trabeculations in the LAA contrasts with the smooth surface of the remaining left atrium. During states of low flow, the greater surface area conferred by the density of trabeculations in the LAA can predispose to thrombus formation. (With permission of the Department of Anatomy and Physiology, University of Toronto, and courtesy of Barbara (Dee) Ballyk, PhD, of the Division of Anatomy and Department of Surgery, University of Toronto, Toronto, Canada.)

morphology, with certain configurations portending a greater stroke risk. There are four known morphologies of the LAA: "chicken wing," "cactus," "windsock," and "cauliflower."[7] The chicken-wing morphology, compared to the other three variant morphologies, has the lowest risk of embolism. The cactus, windsock, and cauliflower morphologies may confer a greater stroke risk as they have lower LAA blood-flow velocities than the chicken-wing morphology. Furthermore large orifice area, ≥3 LAA lobes, and increased LAA trabeculations independently increase stroke risk in AF.[7] Cardiac MRI is emerging as a biomarker of stroke risk in AF as it can visualize and quantify atrial fibrosis, unlike echocardiography. Atrial late gadolinium enhancement on cardiac MRI is associated with ischemic stroke risk.[7]

Cardioversion

Cardioversion (electrical or pharmacologic) undertaken to convert AF back to sinus rhythm is associated with an increased risk of thromboembolism. Patients who have been in AF for 48 hours or more or in whom the duration of AF is unknown are at particular risk. In these individuals, anticoagulation should be started 3 weeks prior to and continued for 4 weeks after cardioversion.

Alternatively, TEE prior to cardioversion can be performed and if no left atrial or LAA thrombus is detected, cardioversion can occur as soon as the patient is anticoagulated. Even in these cases, anticoagulation should continue for at least 4 weeks.[8] If a left atrial thrombus is detected on TEE, anticoagulation is recommended for at least 3 weeks prior to cardioversion and may need to be continued for a longer duration afterward. The recommendations for cardioversion in atrial flutter are the same as for AF.[8]

Cardioversion within the previously acceptable 48-hour window from the time of AF onset may still be associated with a greater risk of cardioembolic stroke, in the vicinity of 0.7 to 1.1 percent.[8] Even a delay of 12 hours or more from time of AF onset to cardioversion is associated with a greater risk of stroke as well. Risk factors for stroke in these settings include female sex, heart failure, diabetes mellitus, and older age. Therefore, the 2019 American Heart Association guidelines suggest that heparin or direct non-vitamin K oral anticoagulants be started prior to cardioversion for those with AF or atrial flutter of less than 48 hours duration with a CHA_2DS_2-VASc score of ≥2 in men and ≥3 in women.[8] Anticoagulation should also be continued after cardioversion in these settings as well. For those with nonvalvular AF or atrial flutter for less than 48 hours, but with CHA_2DS_2-VASc scores of 0 in men and 1 in women, anticoagulation with heparin or direct non-vitamin K oral anticoagulants may be considered prior to cardioversion, without the need for postcardioversion anticoagulation.[8]

Chronic Sinoatrial Disorder (Sick Sinus Syndrome)

Sinoatrial disorder or sick sinus syndrome is due to dysfunction of the heart's sinoatrial (SA) node. This condition manifests as a mixture of bradyarrhythmia, tachyarrhythmia, and chronotropic incompetence. Patients may also have sinus arrest. As such, patients usually presents with syncope, lightheadedness, and exercise intolerance.

There is a higher rate of systemic emboli and AF in those with chronic sinoatrial disorder compared to those with atrioventricular block. Therefore, patients with chronic sinoatrial disorder should be screened closely for AF and, if detected, anticoagulation is usually initiated. In particular, patients with the "brady-tachy" form of the disorder are at higher risk of developing AF and stroke. Studies have not found any difference in stroke risk or mortality whether sinoatrial disorder is managed with single-lead atrial pacing (AAIR) or dual-chamber pacing (DDDR), but prior studies reported a decreased risk of AF with AAIR. Pacing helps with the symptoms of syncope and exercise intolerance and facilitates the detection of AF, but does not reduce stroke risk. Nearly 30 percent of those individuals will have AF at the time of their pacing insertion and by 7 years this increases to 60 percent. DDDR has been demonstrated to reduce the progression of atrial tachyarrhythmias to long-duration and permanent AF in those with sinoatrial disorder.

ATRIAL MYXOMA

Primary cardiac tumors—of which atrial myxomas and papillary fibroelastomas (PFE) are the most common—have a prevalence of 0.05 percent. Histologically, although both atrial myxoma and PFE are benign tumors, they have increased thrombogenic potential, often manifesting with cardioembolic stroke or systemic emboli. Embolic strokes arise either from tumor components or a dislodged thrombus. PFEs technically do not exist in the left atrium and affect the papilla of heart valves, but they are discussed here as they are of equal importance as rare causes of cardiogenic stroke.

Myxomas are more common in women than men and occur in the left atrium in more than 75 percent of cases. Rarely they can obstruct the mitral valve, causing valvular stenosis, which can manifest as exertional dyspnea. Nearly one-third of patients with myxomas have evidence of emboli, including silent brain infarcts. Management is often surgical, but there is a risk of recurrence after incomplete surgical resection. PFEs, while they mostly occur on the aortic and mitral valves, rarely cause valvular incompetence or stenosis. These tumors have fern-like projections from a central stalk and therefore have a large surface area upon which thrombus can form. Surgery is usually indicated for large or symptomatic tumors, whereas close monitoring may be employed for small or asymptomatic tumors.

Interatrial Septum: Paradoxical Embolus

A paradoxical embolus arises when a thrombus formed in the venous system passes into the arterial circulation through a right-to-left shunt such as a PFO, atrial septal defect, or ventriculoseptal defect. Incomplete closure of the foramen ovale in the first few days of life results in persistent PFO in approximately 25 percent of the population. In patients with cryptogenic stroke, a PFO is identified in 40 to 50 percent of cases. The risk of stroke recurrence with a PFO is about 1 to 2 percent per year.[1]

In patients with cryptogenic embolic stroke who are found to have a PFO, it is necessary to determine whether the PFO was responsible or just an innocent bystander given its high population prevalence. A comprehensive stroke work-up is recommended to exclude alternate causes. Factors that increase the likelihood that a PFO is pathogenic include Valsalva maneuver or increased abdominal pressure at the time of stroke onset, younger age and absence of traditional vascular risk factors, recent immobility (surgery; prolonged land or air travel), prior or concomitant venous thromboembolism such as DVT or pulmonary embolism, known hypercoagulable state, history of migraine with aura, pulmonary hypertension, sleep apnea, and stroke occurring during sleep. The probability of a PFO being the causal mechanism of a stroke event can be estimated using the Risk of Paradoxical Embolism (ROPE) score. Certain echocardiographic features of a PFO have been associated with a greater risk of stroke, such as large shunt/PFO size, a hypermobile atrial septum, and atrial septal aneurysm.

There are other fetal structures that can persist into adulthood and may have relevance in cryptogenic stroke. In utero, the right valve of the sinus venosus directs blood flow through the PFO. A Chiari network—a web-like network of fibers—and the Eustachian valve are fetal remnants of the right valve of the sinus venosus, located at the entry point of the inferior vena cava into the right atrium. Approximately 2 to 3 percent of adults have a persistent Chiari network. A Eustachian valve and a prominent Chiari network are common in patients with PFO. A prominent Chiari network is also seen fairly frequently in patients with cryptogenic stroke, and these individuals also tend to have a PFO or atrial septal aneurysm. Together PFOs, Chiari networks, and/or atrial septal aneurysms are associated with cardioembolic stroke. It is hypothesized that the presence of prominent fetal Chiari network and Eustachian valve can direct blood from the inferior vena cava preferentially toward a PFO and may facilitate paradoxical embolization.

Left Ventricle

ACUTE MYOCARDIAL INFARCTION

After myocardial infarction there is an increased risk of stroke that is highest within the first month and persists thereafter. Associated ST segment elevation on the ECG confers a greater risk of stroke than when the ST segment is not elevated. Predictors of stroke following myocardial infarction include advanced age, diabetes, hypertension, previous stroke or myocardial infarction, an anterior myocardial infarct, AF, and heart failure. Mechanisms of cardioembolic stroke in the context of myocardial infarction include (1) left ventricular hypokinesis or akinesis that predisposes to local stasis and formation of mural thrombus and (2) the development of AF, which occurs in up to 20 percent of patients following myocardial infarction.

There is a risk of left ventricular thrombus formation with acute infarction. Patients with large anterior myocardial infarcts associated with a left ventricular ejection fraction less than 40 percent and anterior wall motion abnormalities are at greatest risk of developing mural thrombus in the left ventricle. Left ventricular thrombus develops in about one-third of individuals during the first 2 weeks following an anterior myocardial infarct, posing an even greater risk of embolism. The risk of embolization though decreases after 3 months as thrombus becomes organized, fibrotic, and less mobile.[9]

The overall stroke risk following myocardial infarction has been reported to approximate 1 percent during the first month and about 2 percent at 1 year. This risk may be lower now with modern acute reperfusion interventions and use of anticoagulant therapy.[3] Percutaneous intervention for acute myocardial infarction also bears its own risk of stroke of approximately 0.1 percent.[3]

CARDIOMYOPATHIES

Cardiomyopathies are defined as a heterogeneous group of diseases of the myocardium associated with mechanical or electrical dysfunction (or both) that usually, but not invariably, exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes, frequently genetic. Specifically excluded are those diseases of the myocardium secondary to congenital or valvular heart disease, systemic hypertension, or atherosclerotic coronary disease. The cardiomyopathies are divided into two major groups based on predominant organ involvement. The primary cardiomyopathies are those solely or predominantly confined to heart muscle; genetic, mixed, and acquired forms are recognized. Both hypertrophic and dilated cardiomyopathies are considered primary diseases. Also included are the ion-channel disorders, in which there is a primary electrical disturbance without structural cardiac pathology. These disorders are considered later in relation to syncope.

Secondary cardiomyopathies involve skeletal or smooth muscle in addition to cardiac muscle. Neuromuscular or neurologic causes include Friedreich ataxia, Duchenne or Becker muscular dystrophy, Emery–Dreifuss muscular dystrophy, neurofibromatosis, and tuberous sclerosis. The secondary cardiomyopathy classification does not include infective processes, such as Chagas disease or infection with human immunodeficiency virus, which also cause cardiomyopathy.

In North America, the most common cardiomyopathy is hypertrophic cardiomyopathy, which is an autosomal-dominant disease affecting 1 in 500 persons. It is a major cause of sudden cardiac death in athletes but is compatible with survival until old age. Stroke risk in hypertrophic cardiomyopathy is elevated, with an annual incidence of 0.8 percent.

There are considerable geographic variations in the causes of cardiomyopathy. In Latin America, American trypanosomiasis (Chagas disease) is common. Cardioembolic stroke has been increasingly well documented as a complication, and most occur in the anterior circulation. In Chagas cardiomyopathy, the apical region of the left ventricle is the typical site for formation of thrombosis or aneurysm. Echocardiography reveals an apical aneurysm in one-third of patients and a mural thrombus in about 10 percent. Left ventricular diastolic dysfunction is present in nearly one-half of patients. The ECG is abnormal in two-thirds, including right bundle branch block, left anterior fascicular block, and AF.

Other regional variations include endomyocardial fibrosis restricted to the tropical regions of East, Central, and West Africa. Furthermore, the incidence of human immunodeficiency virus–associated cardiac disease, including cardiomyopathy, is increasing, in contrast to developed countries where the availability of antiretroviral therapy has reduced the incidence of myocarditis.

Patients with dilated cardiomyopathy have an increased incidence of embolic events including systemic embolism and stroke secondary to ventricular mural thrombi, and therefore anticoagulant therapy should be considered for secondary stroke prevention in select cases. Other neurologic manifestations of cardiomyopathies are considered later.

LEFT VENTRICULAR DYSFUNCTION

Patients with ischemic and nonischemic cardiomyopathies are at increased risk of stroke related to left ventricular dysfunction. Left ventricular dysfunction leading to systolic heart failure (also termed heart failure with reduced ejection fraction) is a risk factor for stroke. However, even in the absence of clinically overt heart failure or myocardial infarction, the presence of asymptomatic left ventricular systolic dysfunction is an independent risk factor for intracardiac thrombus formation and stroke.[3]

Congestive heart failure carries a two- to threefold increase in the relative risk of stroke. The mechanism underlying stroke in these cases is multifactorial, related to a hypercoagulable state, concomitant vascular risk factors, regional stasis, and the association between heart failure and AF.[3] Among patients enrolled into heart failure trials, the overall annual stroke risk ranges between 1.3 and 3.5 percent. The left ventricular ejection fraction was inversely associated with cardiovascular mortality up to a value of 45 percent in the Warfarin versus Aspirin in Reduced Ejection Fraction (WARCEF) trial.[10] An ejection fraction of less than 15 percent more than doubles the risk of stroke.[10] Other studies report an increased stroke risk with a left ventricular ejection fraction less than 35 percent.[9]

Valvular Diseases

MITRAL ANNULAR CALCIFICATION

Mitral annular calcification is a common process that arises due to chronic noninflammatory fibrous calcification of the mitral annulus. It is a low-risk potential source of calcific or thrombotic emboli to the cerebral and retinal circulations.[1] The Framingham study documented a doubling of stroke risk in those with mitral annular calcification compared to those without, but it is unclear whether this relationship is causal or a marker for other risk factors such as AF and generalized atherosclerotic disease, including carotid stenosis and calcified aortic arch plaque. Mobile plaques on the mitral annulus, however, do confer a greater risk of embolic potential.

MITRAL VALVE PROLAPSE

Mitral valve prolapse is the most frequent valvular disease in adults, with a prevalence of about 2 percent. In the Framingham cohort, no significant difference was found in the prevalence of stroke or TIA in those with or without it, but other studies have shown a modestly increased incidence of stroke in those with mitral valve prolapse. The estimated risk of stroke with it is 1 per 6000 patient years. The mechanism of stroke with mitral valve prolapse may be related to thrombi forming on the surface of redundant leaflet tissue.

MITRAL VALVE REGURGITATION

Mitral valve prolapse can also be associated with an elevated risk of thromboembolic complications in the presence of mitral valve thickening or mitral regurgitation. Mitral regurgitation can lead to progressive left atrial dilatation leading to the evolution of an aberrant atrial substrate and AF.

Mitral regurgitation can occur in the context of dilated cardiomyopathies, where displaced papillary muscles and annular dilatation impair leaflet coaptation. While there are primary causes of mitral regurgitation, it can also arise in the context of vascular risk factors manifesting as ischemic cardiac disease. Progressive mitral regurgitation begets further left ventricular dilatation and subsequently worsens the regurgitation. Unless AF arises in the context of mitral regurgitation, antithrombotic therapy has not been recommended for stroke prevention. However, with symptomatic regurgitation (heart failure, dyspnea, exercise intolerance), regurgitation volume ≥ 60 ml, left ventricular end-systolic diameter ≥ 40 mm, pulmonary artery systolic pressure >50 mmHg, or new-onset AF, patients may benefit from mitral valve surgery or repair.[8]

MITRAL VALVE STENOSIS AND RHEUMATIC HEART DISEASE

There is a well-established association between stroke and rheumatic heart disease, especially mitral stenosis, and particularly in the setting of AF and atrial thrombus. Rheumatic heart disease is a result of a delayed autoimmune reaction to a streptococcal infection, with molecular mimicry mediating an inflammatory reaction in cardiac valvular tissue. Systemically, patients with rheumatic fever can have arthritis and nephritis as well. Although the incidence of rheumatic heart disease has declined because of prompt antibiotic treatment, in some parts of the world it is an important cause of mitral stenosis, valvular AF, and stroke.

The term “valvular AF” has been used to refer to AF in the context of severe mitral stenosis or a mechanical valve. Guidelines recommend long-term warfarin (target $\text{INR} = 2.5 \pm 0.5$) for patients with rheumatic mitral valve disease who have a history of systemic embolism or who develop chronic or paroxysmal valvular AF.[11] It is also recommended, in the context of severe mitral stenosis, that warfarin be given to patients in normal sinus rhythm if the left atrial diameter is in excess of 5.5 cm, regardless of a history of AF or embolism.

AORTIC VALVE STENOSIS

Aortic valve stenosis or calcification is a minor-risk potential cardiac source of stroke.[1] Aortic valve stenosis can arise secondary to degenerative calcification and rheumatic or congenital pathologies and is associated with aging and vascular risk factors. Systemic embolism in patients with aortic valve disease is uncommon in the absence of AF or other risk factors. Severe and symptomatic aortic valve stenosis is an indication for percutaneous valvuloplasty or valve replacement.

LAMBL EXCRESCENCES

Lambl excrescences are rare fine, mobile, frond-like extensions of cardiac valves that occur at sites of valve closure and arise as a result of endothelial damage with wear and tear. Their appearance on echocardiography may evoke a differential diagnosis that includes vegetations, metastases, fibroelastoma, myxoma, or thrombi. TEE is the best modality with which to visualize them. They are mostly asymptomatic, but their location on and subsequent detachment from aortic or mitral valves can manifest as a cardioembolic stroke. They should be considered in cases of cryptogenic stroke.

PROSTHETIC HEART VALVES

Valvular heart disease necessitating surgical or endovascular valve replacement is fairly common. The risk of thromboembolism in patients with mechanical heart valves is dependent on several factors—the adequacy of anticoagulation, characteristics of the valve (type and location of valve, number of valves), and patient-related risk factors such as AF and others. In general, thromboembolic complications are more common with mechanical valves than bioprosthetic (tissue) valves, more common with mitral than aortic valve replacement, and more common with older- than newer-generation valves. Mechanical valves confer about a 4 percent annual risk of stroke, whereas bioprosthetic valves confer a much lower stroke risk.[3] Anticoagulation with warfarin reduces the annual risk of stroke to 0.8 percent with mechanical aortic valves and 1.3 percent with mechanical mitral valves.[3] Lifelong vitamin K antagonist therapy, such as with warfarin, is recommended for all patients with mechanical valves, and strict INR control is essential for stroke prevention. Published guidelines should be consulted for specific treatment recommendations because INR targets differ for certain valves or patient characteristics, and some guidelines recommend the addition of aspirin. The efficacy of warfarin depends on maintaining a stable therapeutic INR, and this can be challenging because the INR can fluctuate due to illness, drug interactions, diet, and medication adherence. Prosthetic heart valves are also an independent risk factor for infective endocarditis, a major risk cause of cardioembolic stroke.

Endocarditis

INFECTIVE ENDOCARDITIS

Infective endocarditis, discussed in detail in Chapter 6, refers to a bacterial or fungal infection of the endocardium or heart valves. Risk factors for its development include an immune-compromised state (diabetes mellitus, corticosteroid use), injection drug use, invasive procedures, and rheumatologic conditions such as psoriasis. The most common bacteria are Staphylococci, accounting for 60 to 80 percent of cases, but other organisms, such as *Candida*, gram-negative bacilli, and HACEK organisms (*Haemophilus parainfluenza, H. aphrophilus, H. parahrophilus, H. influenza, Actinobacillus actinomycetemcomitans, Cardiobacter hominins, Eikenella, Kingella kingae*) have been implicated as well. Regardless of the pathogen, left-sided endocarditis, affecting the mitral or aortic valves, confers a high risk of embolic stroke. Embolic cerebral ischemic lesions occur in 50 to 80 percent of cases as detected by MRI. Abscesses and mycotic aneurysms with subarachnoid hemorrhage occur in up to 10 percent of cases.

Given the risk of mycotic aneurysm formation and subarachnoid hemorrhage, the administration of acute thrombolytic therapy and anticoagulation may adversely affect outcomes. All febrile patients presenting with acute stroke symptoms should be evaluated urgently for signs of infective endocarditis by clinical examination, echocardiography, and blood cultures. It is prudent to exclude infective endocarditis before administering thrombolytic agents.

MARANTIC (NONBACTERIAL THROMBOTIC) ENDOCARDITIS

Marantic or nonbacterial endocarditis is characterized by sterile fibrin and platelet aggregates or vegetations on heart valves. Compared to infective endocarditis, these vegetations are more friable and prone to embolization, with an incidence of cerebral ischemia of 33 percent compared to 19 percent. There is no associated bacteremia or destruction of heart valves. Marantic endocarditis is not the same as “culture-negative” IE, which can occur in the context of prior antibiotic administration or infection with fastidious bacteria or nonbacterial pathogens. Marantic endocarditis is thought to arise after endothelial cell injury in the context of a hypercoagulable state. Many well-described conditions may be responsible, including antiphospholipid antibody syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, and disseminated malignancy. Echocardiography reveals marantic endocarditis in upwards of 19 percent of metastatic adenocarcinomas, the most common originating from the pancreas and lung.

Clinically, marantic endocarditis can manifest as new cardiac symptoms with progressive dyspnea on exertion, pedal edema, exercise intolerance, constitutional symptoms, and signs of systemic rheumatologic disease, coupled with clinical manifestations of embolization including focal neurologic deficits, flank pain, an acute abdomen, or painful ischemic extremities. The diagnostic work-up in suspected cases includes serial blood cultures to exclude infective endocarditis, TEE to evaluate the mitral and aortic valves, imaging studies to look for occult malignancy, and blood tests for rheumatologic conditions, lupus anticoagulant, and anticardiolipin and anti-B_2-glycoprotein 1 antibodies. Treatment involves unfractionated or low-molecular-weight heparin or warfarin. Those with antiphospholipid antibody syndrome should receive life-long anticoagulation. Embolic stroke secondary to marantic endocarditis in the context of disseminated malignancy is associated with a poor prognosis.

MANAGEMENT OF CARDIOGENIC BRAIN EMBOLISM

Emergency Reperfusion Treatment

THROMBOLYSIS

The administration of intravenous alteplase (tPA) at 0.9 mg/kg within the first 4.5 hours of stroke onset improves functional outcomes and is guideline-recommended for eligible patients with acute ischemic stroke. Patients receiving intravenous tPA have an increased odds of reduced disability and of recovery with no disability at 3 to 6 months after their stroke, but the effectiveness of tPA is time sensitive. According to a 2014 meta-analysis of nine trials of intravenous tPA, the number of patients needed to treat (NNT) for one additional patient to recover without disability is 10 when intravenous tPA is administered within the first 3 hours of stroke onset, and 19 when administered between 3 and 4.5 hours after onset. In contrast, the NNT for one additional fatal intracranial hemorrhage is 40 to 50. Strict eligibility criteria have been established to minimize the risk of hemorrhage. Tenecteplase, another tissue plasminogen activator, is an emerging treatment being investigated for acute ischemic stroke that appears to be as effective as alteplase and may have a lower risk of bleeding.[2,11] Recent trials suggest that intravenous tPA can be effective beyond 4.5 hours in carefully selected patients who have potentially salvageable tissue as defined by CT perfusion studies or MRI.

Endovascular Therapy

Modern endovascular therapy has revolutionized acute stroke treatment and outcomes. Cardioembolic strokes, which often cause large proximal embolic intracranial or extracranial large-artery occlusions, may be amenable to emergency removal by mechanical thrombectomy or direct intra-arterial thrombolysis. The effectiveness of endovascular therapy for improving outcomes after large-vessel occlusions in the anterior circulation has now been firmly established by five randomized trials published in 2015. A pooled analysis of these trials (HERMES collaboration) demonstrates that endovascular therapy within 6 hours of onset doubles the odds of functional recovery without disability.[12]

The advent of CT perfusion imaging permits a more refined selection of patients who may benefit from endovascular therapy for up to 24 hours after stroke onset. A sizable "mismatch" lesion pattern on CT perfusion indicates potentially salvageable tissue. The DEFUSE-3 and DAWN trials established the effectiveness and safety of endovascular therapy for up to 16 or 24 hours after onset, respectively, for highly selected stroke patients with a favorable neuroimaging profile.[11] Mechanical thrombectomy is now recommended for carefully selected patients with acute ischemic stroke who are within 6 to 24 hours of their last known normal time, have a large-vessel occlusion in the anterior circulation, and satisfy DAWN or DEFUSE-3 eligibility criteria.[11]

Stroke Prevention

Anticoagulant Therapy for Atrial Fibrillation

Anticoagulant therapy is highly beneficial for stroke prevention in individuals with AF, reducing the risk of stroke by about two-thirds (Table 5-3).[13–15] Without anticoagulation, individuals with AF have an average annual risk of stroke of 4.5 percent in the absence of a past history of stroke, and 12 percent in those with a previous stroke. With warfarin, there is a 64 percent reduction in the stroke risk. For primary stroke prevention, the absolute stroke risk reduction (ARR) with warfarin is 2.7 percent (NNT, 37), and for secondary prevention the ARR is 8.4 percent (NNT, 12).[14] Ischemic strokes occurring in patients taking warfarin are less severe on average than in those not taking warfarin, with an inverse relationship observed between INR level and stroke severity.

Antiplatelet agents are far less effective than warfarin at reducing the risk of stroke in patients with AF. Aspirin (75 to 1200 mg daily), is associated with a 19 percent relative risk reduction of stroke compared with placebo or no treatment, and has an ARR of 0.8 percent (NNT, 125) for primary prevention and of 2.5 percent (NNT, 40) for secondary stroke prevention.[14] Warfarin as compared with antiplatelet agents is associated with a 37 percent relative reduction in stroke risk.[14] Aspirin's benefit in these patients may be to prevent nondisabling stroke that is not of cardioembolic origin. Therefore, guidelines

TABLE 5-3 ■ Efficacy of Warfarin for Stroke Prevention in Atrial Fibrillation

		Primary Prevention			Secondary Prevention		
	RRR (%)	Annual Stroke Risk (%)	ARR (%)	NNT	Annual Stroke Risk (%)	ARR (%)	NNT
No treatment		4.5			12		
Aspirin vs. placebo or no treatment	19		0.8	125		2.5	40
Warfarin vs. placebo or no treatment	64		2.7	37		8.4	12
Warfarin vs. aspirin	38		0.7	142		7.0	14
		All Stroke Prevention*					
	RRR (%)		ARR (%)	NNT			
DOAC vs. warfarin*	19		0.3	332			

ARR, Absolute risk reduction; RRR, relative risk reduction; DOAC, direct non-vitamin K oral anticoagulants.

*This meta-analysis by Ruff and colleagues did not distinguish between primary and secondary stroke prevention.[15]

Adapted from previously published meta-analyses (Hart RG, Pearce LA, Aguilar MI: Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 146:857, 2007[14] and Ruff CT, Giugliano RP, Braunwald E, et al: Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 383:955, 2014[15]).

strongly recommend anticoagulant therapy rather than aspirin for stroke prevention in eligible individuals with AF. The risk of intracranial hemorrhage is doubled with warfarin compared to aspirin, although the absolute risk increase is 0.2 percent.[14] However, the outcome measure—stroke—in this meta-analysis represented a combination of intracranial hemorrhage and ischemic stroke. Therefore, the reported risk reductions above account for the increased risk of intracranial hemorrhage on warfarin. Compared with placebo, warfarin also reduces all-cause mortality by 26 percent.[14] Warfarin, however, is a difficult medication for patients because of the requirement for INR monitoring, drug and food interactions, fluctuations in INR, and bleeding risks.

Until 2009, warfarin and other vitamin K antagonists were the only type of oral anticoagulation available.[15] The arrival of the direct non-vitamin K oral anticoagulants as an alternative to vitamin K antagonists has represented a major advance in stroke prevention and these agents have now become the preferred anticoagulant treatment for patients with nonvalvular AF. The non-vitamin K oral anticoagulants either directly inhibit thrombin (dabigatran) or factor Xa (apixaban, edoxaban, rivaroxaban).[8] In contrast to warfarin, these drugs have a rapid onset of action, short half-life, fewer drug interactions, lack of food interactions, and do not require INR monitoring.[15] Regular follow-up of patients receiving such therapy is important to review their clinical status, assess and reinforce medication adherence, check blood pressure and renal function, screen for any bleeding concerns or drug interactions, and ensure that dosing is correct. An excellent practical guidance document has been published.[13] Direct non-vitamin K oral anticoagulants are contraindicated in patients with mechanical heart valves and are not recommended in renal failure.

There have been four pivotal phase III randomized trials evaluating the four non-vitamin K oral anticoagulants compared to warfarin in patients with nonvalvular AF. Overall, they are at least as effective if not slightly more effective than warfarin for stroke prevention, have similar or lower rates of major bleeding complications, and have a lower incidence of intracranial hemorrhage. In a meta-analysis by Ruff and co-workers comprising 71,683 patients, non-vitamin K oral anticoagulant therapy was associated with a 19 percent reduction in stroke or systemic embolic events compared with warfarin, mainly driven by a reduction in hemorrhagic stroke.[15] Specific antidotes have been developed and are entering clinical practice. Idarucizumab is a monoclonal antibody fragment that binds to dabigatran and rapidly normalizes hemostasis, and andexanet alfa is a recombinant coagulation factor Xa that can reverse the effects of rivaroxaban and apixaban.

TREATMENT DECISIONS

All types of AF (paroxysmal, persistent, or permanent) should be considered for anticoagulant therapy, unless contraindicated. AF occurring in the postoperative setting following cardiac surgery is fairly common and usually self-limited. Anticoagulation is reasonable if AF persists for more than 48 hours in this setting, but it may not need to be continued on a long-term basis if sinus rhythm is restored. Ongoing studies aim to better define the role of anticoagulation in such patients and it remains necessary to individualize management strategies for specific patients. Risk stratification is essential to determine optimal treatment.

The choice of a vitamin K antagonist or a direct non-vitamin K oral anticoagulant may be guided by a variety of factors including valvular heart disease, patient comorbidities such as kidney disease, concurrent medications, patient-specific bleeding risks, compliance, patient preferences, and cost. Risk stratification for bleeding can be estimated using the HAS-BLED or other scores, which take into account hypertension, renal disease, liver disease, past history of stroke, previous major bleeding episodes, unstable INR, age >65 years, alcohol use, and medications that increase bleeding risk.[13]

Many schemes have been devised for identifying patients with AF at high, moderate, or low risk for stroke. High-risk factors are previous stroke, TIA, or systemic embolism; mitral stenosis; and prosthetic heart valves. Patients at high-risk should be placed on an anticoagulant. Moderate-risk factors include age older than 75 years; hypertension; heart failure; left ventricular ejection fraction less than 35 percent; and diabetes. The $CHADS_2$ and CHA_2DS_2-VASc scores are commonly used to estimate an individual's risk of stroke and practical online tools are publicly available (e.g., www.sparctool.com). Current recommendations from the American Heart Association are that those with nonvalvular AF and a CHA_2DS_2-VASc score greater than 2 in men or 3 in women should be treated with an oral anticoagulant (level of evidence, A).[8]

The direct non-vitamin K oral anticoagulants are recommended over warfarin in eligible patients (level of evidence, A). Regardless of the CHA_2DS_2-VASc score, AF patients with a mechanical heart valve should only receive warfarin as non-vitamin K oral anticoagulants are contraindicated.[8] For patients prescribed warfarin, INR requires regular monitoring, usually on a monthly basis.[8] For those with a CHA_2DS_2-VASc score of 0 in men or 1 in women, it is reasonable to omit anticoagulant therapy (level of evidence, B).[8] Aspirin alone (81 to 325 mg) is considered sufficient for patients without any additional risk factors. Canadian guidelines currently recommend anticoagulant therapy for all individuals with AF who are aged 65 or older, unless contraindications exist. For patients with AF and a CHA_2DS_2-VASc score of 1 in men or 2 in women, anticoagulation may be considered (level of evidence, C). For patients who cannot take long-term anticoagulant therapy, an alternative is a LAA occlusion procedure, which has comparable efficacy to warfarin without the long-term bleeding risks.[2,8,13]

ACUTE MYOCARDIAL INFARCTION

For secondary stroke prevention after a myocardial infarct, current guidelines from the American Heart Association recommend treatment with vitamin K antagonists for patients who have an ischemic stroke or TIA in the context of an acute anterior infarct with an elevated ST segment and anterior or apical akinesis or dyskinesis defined by echocardiography.[9] In those with acute infarct complicated by left ventricular mural thrombus or either anterior or apical wall motional abnormalities and a left ventricular ejection fraction of less than 40 percent, there is an even stronger recommendation for anticoagulant therapy. For patients who are intolerant of vitamin K antagonists, treatment with low-molecular-weight heparin or a direct non-vitamin K oral anticoagulant can be considered.[9]

CARDIOMYOPATHY AND LEFT VENTRICULAR DYSFUNCTION

In patients with ischemic stroke or TIA who have either left atrial or left ventricular thrombus, anticoagulant therapy with vitamin K antagonist is recommended for at least 3 months (level of evidence, C).[9] In the WARCEF randomized trial of 2305 patients with heart failure (left ventricular function $\leq 35\%$) and in sinus rhythm, warfarin reduced the risk of ischemic stroke but the benefit was offset by an increase in major bleeding.[10] In a meta-analysis of patients with congestive heart failure with reduced ejection fraction, there was a small absolute reduction in the risk of ischemic stroke in those treated with warfarin rather than antiplatelet therapy, but this was accompanied by an increased risk of major hemorrhage (mostly intracranial) and was not associated with any accompanying reduction in death, myocardial infarction, or hospitalization due to heart failure. In the COMMANDER HF trial of patients with reduced left ventricular ejection fraction (40%) in sinus rhythm, rivaroxaban at a dose of 2.5 mg twice daily was not associated with a significantly lower rate of the composite outcome of death, myocardial infarction, or stroke compared with placebo, although stroke events were reduced.

PATENT FORAMEN OVALE

The treatment options for secondary stroke prevention after a presumed PFO-related ischemic stroke are: (1) percutaneous PFO device closure plus long-term antiplatelet monotherapy; (2) anticoagulant therapy; or (3) antiplatelet therapy alone. Six randomized controlled trials have compared PFO closure with medical therapy. There is strong evidence that PFO closure is more effective than antiplatelet therapy alone.[16,17] Guidelines recommend PFO closure for secondary stroke prevention in patients aged 18 to 60 years (up to age 65 years in one guideline), but careful patient selection is essential. PFO closure should only be recommended for patients with an embolic stroke event for which there is a high probability of a causal role for the PFO and a comprehensive etiologic work-up has excluded other causes. PFO closure is not recommended for primary stroke prevention.

In an analysis by Saver and colleagues, the NNT with PFO closure to prevent one recurrent ischemic stroke over 5 years is 24 overall; NNT was 18 for moderate to large shunts, and 13 for PFOs associated with an atrial septal aneurysm.[16] According to a 2018 meta-analysis and guideline, for every 1000 patients treated, there will be 100 recurrent strokes over 5 years with antiplatelet therapy alone, 29 with anticoagulant therapy, and 13 with PFO closure.[17] PFO closure is associated with a 3.6 percent incidence of procedural complications plus a 3 percent increase in the risk of developing AF (transient in about half the cases). Long-term anticoagulant therapy is associated with increased bleeding risks.[17]

For patients who do not undergo PFO closure, either antiplatelet or anticoagulant therapy is reasonable. Anticoagulant therapy is probably better, although the evidence for this recommendation is weak because randomized trial data are limited.[17]

Clinicians should help patients understand the benefits and risks of each of the treatment options using a shared decision-making approach and taking into account patient values and preferences. Useful patient decision aids are available (https://app.magicapp.org/app#/guideline/2649).[17]

SYNCOPE

Syncope is a transient loss of consciousness associated with an inability to maintain postural tone and with rapid spontaneous recovery.[18] It is due to generalized cerebral hypoperfusion in the context of cardiac, neurologic, vasovagal, hypovolemic, or psychogenic causes. Syncope is discussed in detail in Chapter 8, but is considered here with regard to its occurrence in patients with acquired cardiac disease and arrhythmias.

Clinical Manifestations

The clinical spectrum of abnormalities that occur with generalized cerebral hypoperfusion is broad, ranging from nonspecific "dizziness" to a variety of disturbances including paresthesias, visual alterations, loss of consciousness, and sometimes even convulsive movements. Syncope and seizure can therefore be difficult to differentiate clinically. Patients with syncope often report feeling distant, dazed, or as if they are "fading out" before losing consciousness. Motor activity is common, with generalized tonic contraction of axial muscles followed or accompanied by irregular nonrhythmic jerking of the extremities; generalized rigidity without clonic activity; or irregular facial movement or eyelid flutter without tonic activity. Myoclonic activity, head turns, oral automatisms, and writhing movements also occur rarely in syncope. Upward deviation of the eyes is common. During recovery, tonic flexion of the trunk may occur and patients may be dazed or confused for up to 30 seconds after restoration of the circulation. Typically though, there is an abrupt restoration of consciousness and cognition, in contrast to generalized seizures.

Certain clinical features can help to differentiate seizure from syncope, as summarized in Table 5-4. Syncope is especially common in the elderly, who show a high recurrence rate. Of the many causes of syncope, it is important to identify those of cardiac origin because mortality is significantly increased in this group of patients.

Cardiac Etiologies

Table 5-5 highlights the historical features distinguishing cardiac and noncardiac causes of syncope.[18] Cardiac causes can relate to arrhythmias, structural abnormalities, or both.

STRUCTURAL HEART DISEASE

Syncope can occur in patients with known heart disease. The most common valvular cause of syncope is aortic stenosis, which can cause syncope and dyspnea on exertion. In aortic stenosis, hemodynamic compromise mediates syncope due to an inability to sustain cardiac output across a fixed area of critical stenosis. Aortic valve replacement or repair is recommended in these individuals.[18]

Obstruction of the left ventricular outflow tract can also cause syncope. One cause is hypertrophic cardiomyopathy if the outflow tract comes to be obstructed, leading to syncope by one of two mechanisms. Exertional syncope may occur because of the obstructed outflow, or syncope may relate to left ventricular dilatation and heart failure predisposing to malignant arrhythmias and sudden cardiac death.[18] In addition to common structural causes, aortic tract outflow stenosis or intermittent obstruction to outflow may occur, for example, by a mobile thrombus or tumor in the left atrium or ventricle.

A rare cause of cardiac syncope is cardiac sarcoidosis, in which a number of mechanisms may be operative. Macro-reentrant arrhythmias surrounding granulomas are the most common form of ventricular arrhythmia in this context, but cardiac myocyte inflammation can compromise left

TABLE 5-4 ■ Clinical Features to Differentiate Generalized Seizures from Syncope

	Seizures	Syncope
Patient characteristics	Past history of seizures History of head trauma History of febrile seizures History of developmental delay	Severe anemia or gastrointestinal bleeding Cardiac disease Autonomic neuropathy Medications (eg., antihypertensives)
Before the event	Stereotyped prodrome May have speech arrest, sense of impending doom, epigastric sensation, sensory aura, and/or automatisms	May not have a prodrome If prodrome present, usually of lightheadedness or diaphoresis There may be situational triggers
During the event	Loss of consciousness Lasts seconds to minutes May have forced lateral eye or head deviation; repetitive stereotyped movements; or rhythmic clonic activity Incontinence is common	Loss of consciousness Lasts seconds (if patient falls flat) Nonrhythmic movements Incontinence may occur
After the event	Prolonged postictal confusion and behavioral disturbances (minutes or hours) Lateral tongue laceration	Rapid recovery to cognitive baseline within seconds
Neurologic findings	Focal neurologic deficit (Todd paresis) may persist after the episode	No focal neurologic deficits
Investigations	EEG may demonstrate epileptiform activity*	Hypotension and bradycardia may occur during tilt-table testing ECG and Holter abnormalities may suggest arrhythmia Structural cardiac disease may be found on echocardiography

*EEG, electroencephalogram. An EEG is not routinely ordered in the work-up of syncope unless there are accompanying neurologic features to suggest seizure.

TABLE 5-5 ■ Features Associated with Cardiac and Noncardiac Causes of Syncope

Cardiac	Noncardiac
Age > 60 years	Younger age
Male	No known cardiac disease
Presence of cardiac disease (ischemic, structural, prior arrhythmias, or reduced left ventricular ejection fraction)	Positional (from supine/sitting to standing)
Syncope on exertion	Presence of prodrome: nausea, vomiting, feeling warmth
Syncope in supine position	Triggers: dehydration, stress, distressing stimulus, medical environment, cough, laugh, micturition, defecation, deglutition
Low number of syncopal episodes	Frequent recurrence with similar characteristics
Abnormal cardiac examination	
Family history of inheritable conditions	
Family history of sudden cardiac death before 50 years of age	

Adapted from the 2017 American College of Cardiology and American Heart Association Guidelines on the evaluation and management of patients with syncope.[18]

ventricular function, affect the electrical automaticity of myocytes, and predispose to arrhythmia such as ventricular fibrillation.[18] Furthermore, varying degrees of atrioventricular conduction blocks are common in cardiac sarcoidosis.[18] The best method for evaluation of sarcoid is by cardiac MRI; the syncope is best managed with implantable cardiac defibrillators.[18]

Other rare and acquired cardiomyopathies (infiltrative, mitochondrial, and infectious etiologies) are associated with cardiogenic stroke and in some instances can present with syncope as well. There are a group of patients with syncope and a structurally normal heart who pose a particular diagnostic challenge and raise the possibility of additional disorders of the conducting tissues, including channelopathies.

ARRHYTHMIAS: CONDUCTION ABNORMALITIES

Bradyarrhythmias are commonly due to sinus node dysfunction (sick sinus syndrome) or AV nodal conduction diseases. Ischemic cardiomyopathy can cause second- and third-degree atrioventricular conduction blocks that can cause bradyarrhythmias and syncope, and rare infiltrative diseases such as cardiac amyloidosis and sarcoid can do so as well.[18] Stokes–Adams attacks are sudden, brief (10 to 30 seconds) episodes of loss of consciousness, sometimes accompanied by motor activity, that are typically caused by complete third-degree atrioventricular block, which can be seen on the ECG during an attack. Heart rate during an episode is markedly slow. Although coronary artery disease is a common etiology in older individuals, young individuals with congenital heart block may also experience attacks.

Supraventricular tachycardia seldom causes syncope, except in elderly subjects or in young persons with an extremely rapid tachycardia. A relatively common disorder predisposing to paroxysmal supraventricular tachycardia is Wolff–Parkinson–White syndrome. This occurs in the context of an accessory electrical pathway leading to a supraventricular tachycardia, which is usually sporadic with a prevalence of up to 1 in 1,000 persons.[18] AF may develop, and "dizziness," syncope, and, rarely, sudden death may occur. The characteristic ECG hallmarks are a short PR interval and a slowly rising prolonged QRS complex. Management may involve accessory pathway ablation.

Patients with a ventricular arrhythmia (fibrillation or tachycardia) experience syncope after 9 seconds regardless of whether the arrhythmia is sustained. The arrhythmia can be monomorphic or polymorphic. When a patient reports light-headedness with palpitations, ventricular tachycardia must be considered as a possible etiology.[18] Prolonged QT syndrome is considered in the next section.

ARRHYTHMIAS: CHANNELOPATHIES

Channelopathies are a major cause of cardiac-related syncope in young people and are associated with a family history of sudden cardiac death.[18] The possibility of a channelopathy must be considered in a young person with exertional syncope. There are 16 genotypes of long QT syndrome (LQTS) all of which are hereditary channelopathies, with more than 60 percent of cases associated with a loss-of-function mutation in either *KCNQ1* (LQTS type 1) or *KCNH2* (LQTS type 2) potassium channel genes. Exertion or emotion may trigger syncopal events. The characteristic feature is a prolonged QT interval (corrected for heart rate) ≥ 500 msec on a standard ECG. The disorder predisposes to polymorphic ventricular tachycardia, which, in turn, predisposes to syncope and sudden death.[18] More commonly, long QT syndrome occurs as an acquired nongenetic disorder in the context of drugs known to prolong the QT interval. In contrast, a short QT interval syndrome is another genetic condition characterized by palpitations, syncope, and sudden cardiac death with a $\text{QTc} \leq 349$ msec that predisposes to ventricular fibrillation.

Another channelopathy is catecholaminergic polymorphic ventricular tachycardia, which is characterized by catecholamine-induced bidirectional or polymorphic ventricular tachycardia. Approximately 60 percent of patients have a mutation in the cardiac ryanodine receptor (*RyR2*; autosomal dominant) or cardiac calsequestrin gene (*CASQ2*; autosomal recessive).[18] The prevalence is around 0.1 per 1,000. The disorder usually presents in the first or second decade of life with stress-induced syncope. Both this disorder and LQTS-type 1 are best evaluated by cardiac stress test with concurrent ECG recording as they are adrenergically mediated arrhythmias.[18]

Another genetic disease characterized by an increased risk of sudden cardiac death and syncope is Brugada syndrome, which also can produce malignant arrhythmias. Approximately 30 percent of patients have a mutation in *SCN51*, which encodes for cardiac sodium channels. Mutations in *SCN51* alter the function of the channel, ultimately reducing sodium influx into cardiac myocytes and leading to ventricular arrhythmias. It has a higher prevalence in males and in those from Asian countries compared to North America or Northern

Europe. This condition is synonymous with sudden unexplained nocturnal death syndrome (SUNDS). The baseline ECG may be abnormal and show ST elevation in leads V1 and V2, together with a right bundle branch block pattern. This ECG pattern may be concealed and require unmasking by the use of sodium channel blockers.

Evaluation of syncope requires attention to family history including unexplained sudden deaths, age of onset, note of apparent epileptic disorders, relation of events to exertion and distress, and effects of postural change. In the presence of an apparently normal heart, evaluation of the standard ECG, prolonged ECG monitoring, or exercise stress tests may reveal a cause.

CARDIOMYOPATHIES WITH ASSOCIATED NEUROLOGIC MANIFESTATIONS

Cardiomyopathies are mechanical or electrical diseases of the myocardium not caused by valvular heart disease, systemic hypertension, or atherosclerotic coronary disease. They can be inherited or acquired. Many classification systems exist and one phenotypic system classifies cardiomyopathies as (1) dilated, (2) restrictive, (3) hypertrophic, (4) left ventricular noncompaction, and (5) arrhythmogenic right ventricular cardiomyopathy.[19] Most cardiomyopathies are genetic, but secondary etiologies include infectious, infiltrative, inflammatory, nutritional, metabolic, and toxic causes.

While syncope and cardioembolic stroke can occur in the context of ventricular dysfunction from either inherited or acquired cardiomyopathy, the different causes of cardiomyopathy are associated with unique neurologic symptoms ranging from seizures to ataxia to peripheral neuropathy. Recognizing these neurologic manifestations in the presence of clinical and echocardiographic evidence of a cardiomyopathy may help guide clinicians in the differential diagnosis and diagnostic work-up.[19]

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CHAPTER

6

Neurologic Manifestations of Infective Endocarditis

STEVEN M. PHILLIPS ■ LINDA S. WILLIAMS

EPIDEMIOLOGY OF NEUROLOGIC COMPLICATIONS
PATHOPHYSIOLOGY OF NEUROLOGIC COMPLICATIONS
RISK FACTORS FOR NEUROLOGIC COMPLICATIONS
  Site of Infection
  Infecting Organism
  Acuity of Infection
  Valvular Vegetations
  Hematologic Risk Factors
ISCHEMIC AND HEMORRHAGIC STROKE
  Clinical Presentation
  Seizures
  Evaluation of Patients
    Brain Imaging
    Vascular Imaging
    Cerebrospinal Fluid Examination
    Echocardiography
TREATMENT OF ISCHEMIC STROKE
  Antibiotic Therapy
  Thrombolysis
  Antiplatelet and Anticoagulant Therapy
    Anticoagulation in Native Valve Endocarditis
    Anticoagulation in Prosthetic Valve Endocarditis
  Surgical Treatment
TREATMENT OF HEMORRHAGIC STROKE
  Intraparenchymal Hemorrhage
  Mycotic Aneurysms
CEREBRAL INFECTION
  Clinical Presentation
  Evaluation
  Treatment of Cerebral Infection
OTHER NEUROLOGIC COMPLICATIONS
SUGGESTED MANAGEMENT ALGORITHM
PROGNOSIS
CONCLUDING COMMENTS

The relationship between infection of the heart valves and arterial embolization was first recognized by Rudolf Virchow in the mid-1800s and the classic clinical triad of fever, heart murmur, and hemiplegia was described 30 years later by Osler in his Gulstonian Lectures of 1885. Despite an increasing prevalence in recent decades of prosthetic valve and device-related infective endocarditis (IE),[1] the proportion of patients with IE and neurologic manifestations has remained relatively constant. Neurologic complications are frequent and are often associated with increased morbidity and mortality in IE. Although the key to treating neurologic complications is appropriate antibiotic therapy, the presence of neurologic manifestations often alters the medical or surgical treatment of IE.

EPIDEMIOLOGY OF NEUROLOGIC COMPLICATIONS

Neurologic events have long been recognized as frequent and severe complications of IE. Large prospective cohort studies, including the International Collaboration on Endocarditis, and the European Infective Endocarditis Registry provide evidence regarding IE and its various complications.[2–5] The overall frequency of neurologic complications of IE has remained relatively constant at approximately 15 to 30 percent (Table 6-1), and clinically silent cerebral embolism on presentation may occur in nearly half of these cases.[2] Nevertheless, due to the high overall incidence of stroke in the general population, IE is an unusual cause of stroke. Neurologic complications of IE can be divided into three major types:

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TABLE 6-1 ■ Common Neurologic Complications in Patients with Infective Endocarditis

Series	*n*	Ischemic Stroke (%)	Hemorrhage (%)	Primary Infection (%)	All Neurologic Complications (%)*
Garcia-Cabrera 2013	1,345	14	4	7	25
Rizzi 2014	1,456	15*	2	NR	17
Munoz 2015	1,804	NR	NR	NR	20
Habib 2019†	3,119	27	7	NR	NR

NR, not reported.
*Includes transient ischemic attack.
†Reporting does not distinguish cases with potentially more than one cerebral event so estimates may be inflated. Ischemic stroke includes cerebral embolism on admission, and cerebral embolism/TIA/stroke in follow-up. Hemorrhage includes hemorrhagic stroke on admission and follow-up and cerebral hemorrhage in follow-up.

ischemic stroke, hemorrhagic stroke, and direct cerebral infection. Ischemic stroke is by far the most common, accounting for 50 to 75 percent of all neurologic complications. Primary hemorrhage, usually intraparenchymal or subarachnoid, is less common, reported in less than 10 percent of patients. Mycotic aneurysms are reported in less than 2 percent of cases in most cohort studies, although studies that include angiography for all patients report a much higher proportion.[6] Cerebral infections may manifest, without previous clinical evidence of ischemic or hemorrhagic stroke, in less than 10 percent of cases; typical infectious complications include cerebritis, meningitis, and micro- or macroabscesses. Other neurologic symptoms, including seizures, headache, mental status changes, and neuropsychologic abnormalities, sometimes occur but are usually secondary to one of the three major complications. Rarely, endocarditis has been associated with spinal cord infarction or abscess, discitis or spondylitis (4.7% in one series), retinal ischemia, and ischemic cranial and peripheral neuropathies.[2]

PATHOPHYSIOLOGY OF NEUROLOGIC COMPLICATIONS

Almost all the neurologic complications of IE have embolization as their primary cause (Fig. 6-1). Although cerebral emboli are probably not more common than extracerebral emboli, they are more often symptomatic and thus typically reported more frequently; they are also associated with an increased morbidity and mortality compared to other systemic emboli. In general, cerebral emboli most often affect the middle cerebral artery (MCA) territory and may be septic or nonseptic. In patients without neurologic symptoms, MRI shows cerebral lesions in at least 50 percent of cases, and the majority of these are ischemic.[7] Therefore, neuroimaging should be considered in all patients with IE, regardless of neurologic symptoms. Septic emboli may also lead to hemorrhagic stroke through the development of arteritis or mycotic (infectious) aneurysm; cerebral micro- or macroabscess (Fig. 6-2), usually via seeding of ischemic tissue; and cerebritis or meningitis by seeding the meninges.

Most primary intracerebral hemorrhages in IE result from septic embolism followed by septic necrosis and rupture of the vessel wall. Less commonly, they result from rupture of mycotic aneurysms.[2,3] Intracerebral hemorrhage may also occur owing to a secondary hemorrhage into an ischemic infarct (Fig. 6-3).

Mycotic aneurysm formation has been related to (1) septic embolization to the arterial lumen or the vasa vasorum; (2) direct extension from an infection outside the vessel wall; (3) bacteremia causing direct infection of the intima; or (4) direct contamination during surgery or trauma.[8] Mycotic aneurysms are usually small, located at distal arterial bifurcations rather than the circle of Willis, and can be single or multiple. Branches of the MCA are the most common location for mycotic aneurysms (Fig. 6-4).

Brain macroabscesses account for less than 1 percent of all neurologic complications of IE and may occur secondary to ischemic infarction from a septic embolus or from extension of infection from adjacent arteritis or mycotic aneurysm. Brain microabscesses are more common than macroabscesses, are often associated with *Staphylococcus aureus* infections, and usually occur in cases with multiple ischemic infarctions from distal migration

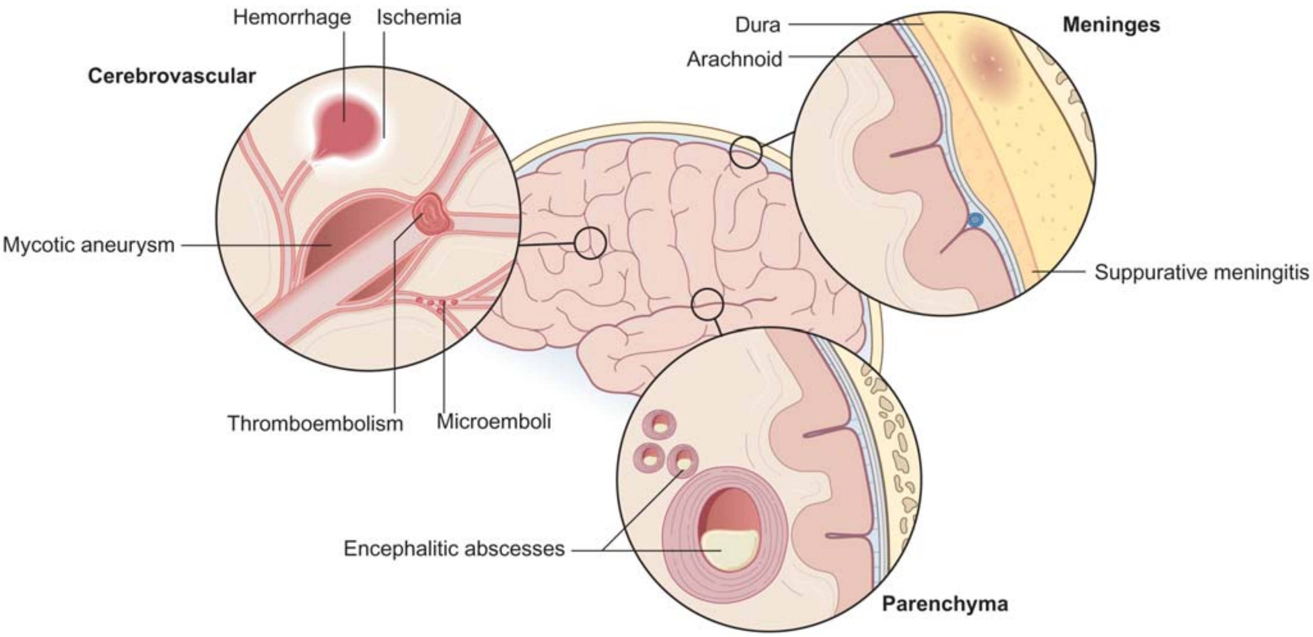
Hemorrhage
Ischemia
Cerebrovascular
Mycotic aneurysm
Thromboembolism
Microemboli
Dura
Arachnoid
Meninges
Suppurative meningitis
Encephalitic abscesses
Parenchyma

FIGURE 6-1 ■ Embolization to various cerebral structures is responsible for most of the neurologic complications of IE. Emboli that lodge in the lumen of cerebral vessels may lead to ischemic stroke and can lead to arteritis or mycotic aneurysm formation with resultant vessel rupture and cerebral hemorrhage. Emboli to the meninges may produce meningitis, and emboli to the brain parenchyma, especially when associated with cerebral ischemia, may result in meningoencephalitis or abscess. (From Solenski NJ, Haley EC Jr: Neurologic complications of infective endocarditis. p. 331. In Roos KL (ed): Central Nervous System Infectious Diseases and Therapy. Marcel Dekker, New York, 1997, with permission. Granted via Copyright Clearance Center.)

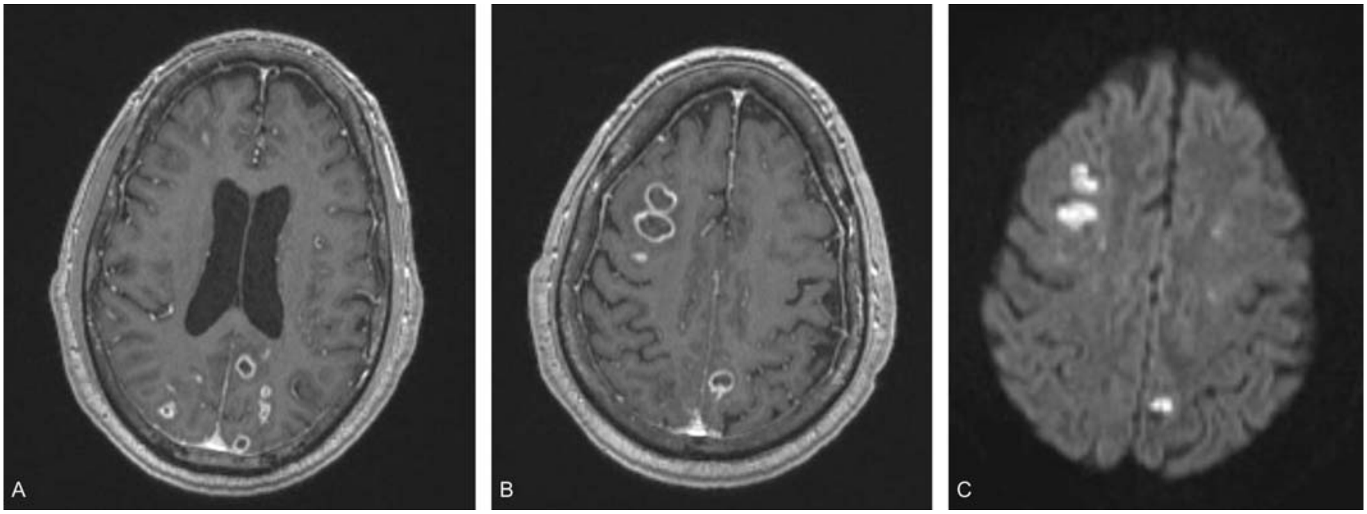

FIGURE 6-2 ■ This patient presented with fever, new cardiac murmur, mental status changes, and right hemiparesis. *A* and *B*, Contrast-enhanced axial T1-weighted magnetic resonance imaging (MRI) shows multiple ring-enhancing lesions suggesting septic microembolization. *C*, Axial diffusion-weighted imaging (DWI) sequences show restricted diffusion associated with the lesions.

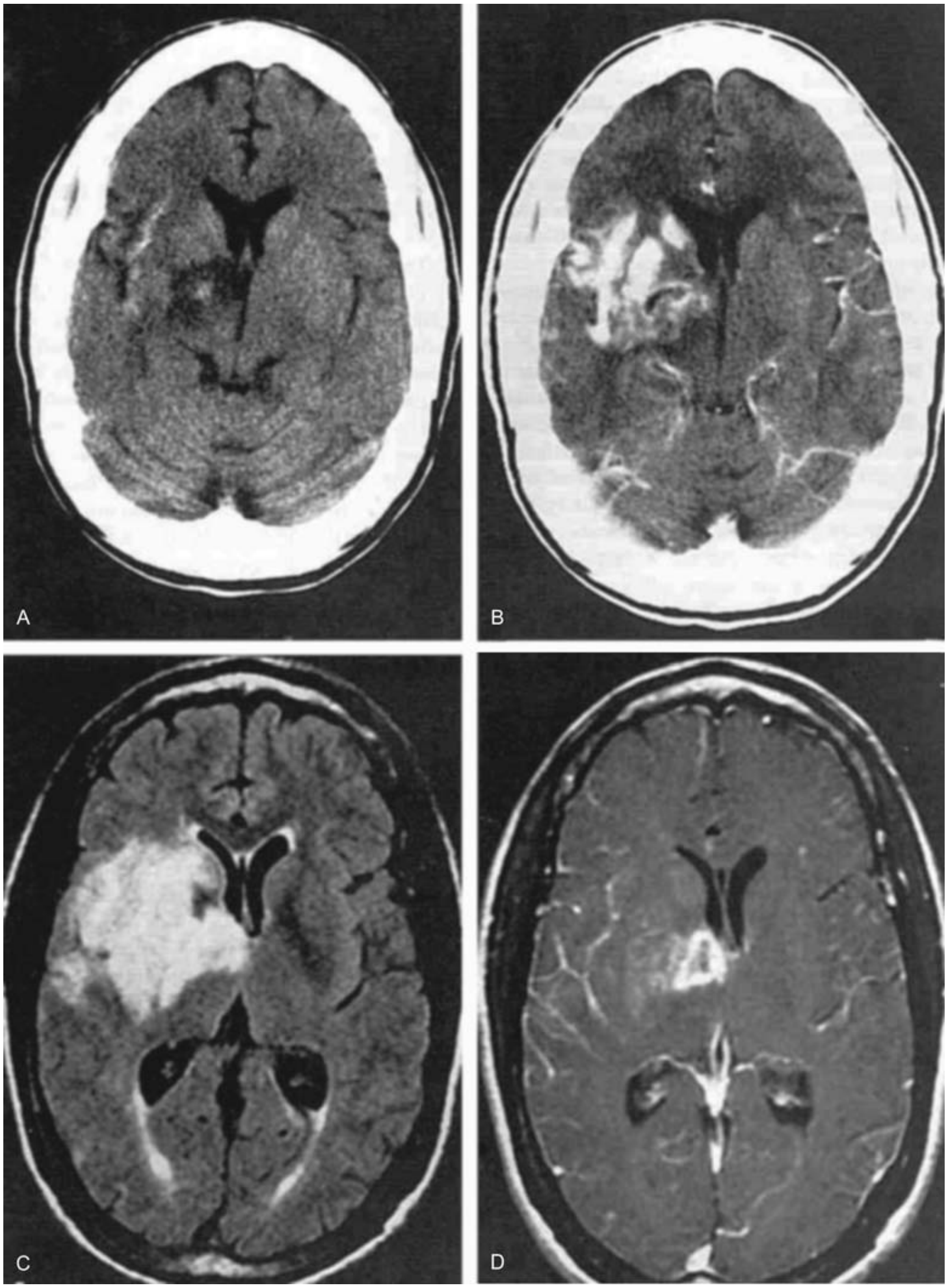

FIGURE 6-3 ■ This patient presented with left hemiparesis and mitral valve endocarditis. *A*, Noncontrast head CT showed a focal low-density lesion in the right internal capsule and lentiform nucleus with a central area of hemorrhage (increased density) and cortical hemorrhage in the insula. *B*, With contrast, large confluent areas of enhancement representing leaky blood–brain barrier can be seen in the right caudate and lentiform nuclei, the insula, and the temporal cortex. *C*, Fluid-attenuated inversion recovery (FLAIR) MRI 2 days after the head CT showed diffuse increased signal in the regions of CT enhancement and the right thalamus. *D*, Following gadolinium administration, ring-like enhancement in the area of a previous infarct can be seen, representing possible secondary infection. This pattern is sometimes referred to as a "septic infarction." This enhancement pattern resolved with antibiotic treatment and without development of a macroabscess.

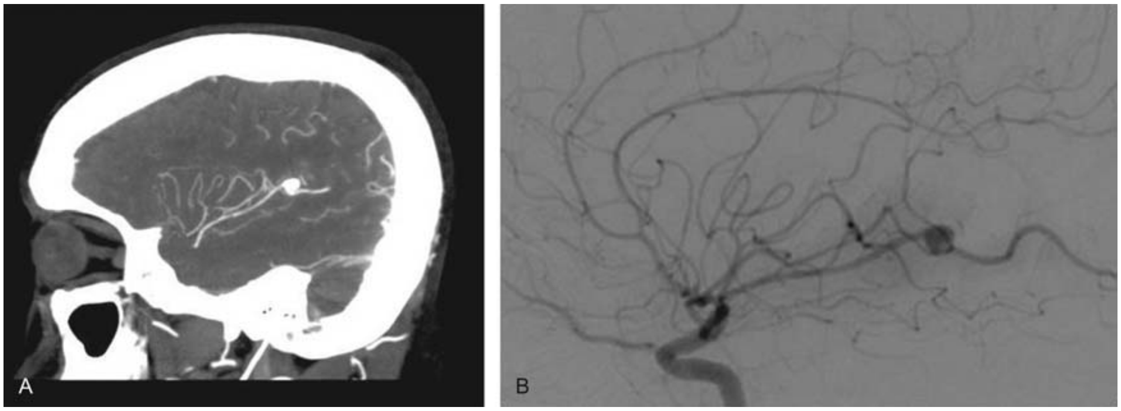

FIGURE 6-4 ■ This patient presented with fever, new systolic murmur, sudden headache, and altered mental status without focal neurologic deficits. Noncontrast head CT showed a small subarachnoid hemorrhage (not shown). Sagittal CT angiogram, *A* demonstrated a mycotic aneurysm in the distal MCA, confirmed by conventional angiography, *B*. This aneurysm enlarged despite adequate antibiotic therapy, and the patient subsequently underwent successful clipping.

of septic embolic fragments. Meningoencephalitis is usually a result of direct embolization to meningeal vessels, with subsequent parenchymal or cerebrospinal fluid (CSF) invasion of the infecting organism. Aseptic meningitis may also occur with subarachnoid hemorrhage due to a necrotic arteritis or ruptured mycotic aneurysm.

RISK FACTORS FOR NEUROLOGIC COMPLICATIONS

A variety of clinical and laboratory features have been associated with an increased risk of embolism or neurologic complications from IE (Table 6-2).[9–11]

Site of Infection

Neurologic complications are more common with left-sided IE than with right-sided valve involvement, although embolization to any organ may be more common with right-sided endocarditis.[2,3,5] Cerebral embolization in right-sided endocarditis may occur through a patent foramen ovale or a pulmonary arteriovenous fistula. Most reports comparing native and prosthetic valve endocarditis indicate no significant difference in the proportion of patients with neurologic complications. Among those with prosthetic valve endocarditis, however, mechanical valves may be associated with complications more often than bioprosthetic valves.

Infecting Organism

Streptococci, staphylococci, and enterococci are the three most prevalent infecting organisms. Both United States nationwide and multicenter European studies found *S. aureus* to be the most commonly identified organism, increasing in the United States from 38 percent in 1998 to 49 percent in 2009.[1,2] In one United States study, 53 percent of the *S. aureus* cases were meticillin-resistant. This changing resistance pattern is reflected in updated treatment guidelines.[9,10]

In most studies, *S. aureus* infection is independently associated with an increased risk of embolization;

TABLE 6-2 ■ **Suggested Risk Factors for Embolization in Infective Endocarditis**

Risk Factor	Proposed Mechanism
Mitral valve infection	Increased valve mobility and left-sided position predispose to cerebral embolization
"Virulent" organism	More rapid endothelial invasion leads to more friable, unstable valve surface
Acuteness of infection	More rapid endothelial invasion leads to more friable, unstable valve surface; acute infection is associated with hematologic factors that may promote thrombosis
Valvular vegetations	Increasing vegetation size and vegetation mobility may predispose to embolism
Hematologic factors	Increased endothelial cell activity, platelet aggregability, and antiphospholipid antibodies may be associated with increased risk of embolization

some authors have reported *Streptococcus bovis* and *Candida* species are also more likely to be associated with embolism.[1,2] It is unclear whether antibiotic susceptibility changes affect the risk of embolic complications, although infections that take longer to control might theoretically have an increased risk of embolization. The virulence of the organism, the availability of effective antimicrobial therapy, and the potential development of large, friable vegetations all contribute to the propensity for embolization.

Acuity of Infection

There is a higher risk of neurologic complications with acute endocarditis than with subacute endocarditis, probably relating to the specific typical etiologic agents noted in acute disease (*S. aureus* and β-hemolytic streptococci) and the potential for large vegetations or valve damage acutely. The risk of cerebral embolization is highest in the first week of infection. Once effective antibiotic therapy is started there is a steep decline in the rate of embolization to 15 percent in the first week and only 4 percent in the second week after antibiotics.[5]

Valvular Vegetations

Detection of valvular vegetations by either transthoracic (TTE) or transesophageal echocardiography (TEE) is a key step in diagnosing IE and also critical to patient management. Because of its increased sensitivity and ability to evaluate the more posteriorly located aortic valve, TEE appears to be cost-effective as the initial study when clinical suspicion of IE is high, but management algorithms often recommend TTE as the initial study because it can be obtained more quickly and it also shows other cardiac abnormalities important in medical and surgical decision-making.[9,10] Most studies have linked the presence of vegetations, especially increased vegetation size (often dichotomized at >10 mm), to an increased risk of embolization.[2,3,5,11,12] A meta-analysis of 21 cohort studies suggested that in addition to size greater than 10 mm, the presence of any vegetations, multiple or mobile vegetations, and vegetations on prosthetic valves were independently related to risk of embolism.[12] Current recommendations suggest that repeat echocardiography may be useful if clinical changes that suggest treatment failure occur during antibiotic therapy and that it should be performed urgently for unexplained progression of heart failure, new heart murmurs, or the development of atrioventricular block.[9,10]

Hematologic Risk Factors

Antiphospholipid antibodies have been associated with IE, and have also been reported to decrease after successful treatment of IE. A recent meta-analysis also found that elevated C-reactive protein was an independent risk for embolism among patients with IE.[11]

ISCHEMIC AND HEMORRHAGIC STROKE

Ischemic stroke secondary to embolization of friable valvular material is the most common neurologic complication of IE. Ischemic stroke is the presenting symptom of IE in up to 20 percent of cases and is most common in the acute stage of the infection, especially prior to or during the first week of therapy.[5] Because of this clustering of symptoms in the acute phase, transient focal neurologic symptoms in a febrile patient, especially in the presence of a regurgitant murmur, should always raise suspicion of IE.

Intracerebral hemorrhage in IE may be primary or secondary to ischemic stroke or other pharmacologic or hematologic conditions (Table 6-3). Of the primary hemorrhages, intraparenchymal and subarachnoid

TABLE 6-3 ■ Causes of Intracerebral Hemorrhage in Infective Endocarditis

- Primary Intracerebral Hemorrhage
    - Arterial rupture secondary to arteritis
    - Rupture of a mycotic aneurysm
- Secondary Intracerebral Hemorrhage
    - Hemorrhagic conversion of ischemic stroke
    - Anticoagulation
- Hematologic Disorder
    - Disseminated intravascular coagulopathy
    - Thrombocytopenia
    - Vitamin K deficiency
- Pre-existing central nervous system lesion (e.g., aneurysm, arteriovenous malformation)

hemorrhage are most common. In one series, only eight cases of subarachnoid hemorrhage occurred among 60 patients with IE and cerebral hemorrhage.[3] Mycotic aneurysms are infrequently reported in large cohort studies, but are estimated to be present in nearly one-third of patients with left-sided IE (26 of 81 consecutive patients with CT angiography, although 15 of the 26 were clinically asymptomatic).[6]

Other conditions that sometimes accompany IE may also predispose to bleeding, including disseminated intravascular coagulation, thrombocytopenia, and vitamin K deficiency. Although mycotic aneurysms are most commonly found in the intracranial vessels, rarely these aneurysms may involve the extracranial carotid, thoracic, or abdominal vessels.[8]

Clinical Presentation

In accordance with their embolic etiology, the majority of ischemic strokes involve the cortex rather than subcortical brain tissue, although finding multiple small emboli that are both cortical and subcortical in location is not uncommon (Fig. 6-5). Patients with multiple microemboli can present with nonlocalizing symptoms, including headache, diminished level of consciousness, encephalopathy, or psychosis (Fig. 6-5). Clinical worsening of ischemic stroke may result from a variety of mechanisms, including development of cerebral edema, recurrent embolization, secondary hemorrhage into the ischemic area, and development of cerebral abscesses. Cerebral edema may occur regardless of ischemic stroke mechanism, is more likely to be symptomatic in larger strokes and in younger patients, and is typically maximal between 3 and 5 days after stroke. Recurrent embolization should be suspected when new focal deficits develop; this complication is most likely to occur early in the course of treatment or when infection is uncontrolled.[5] Hemorrhagic transformation of an ischemic stroke may occur, and may theoretically be more likely in strokes caused by infective endocarditis due to the resulting arteritis. Hemorrhagic transformation of an ischemic stroke is often asymptomatic, as are cerebral microhemorrhages, although development of a large intra-infarct hematoma may be symptomatic. The term "septic infarction" has been used when, several days to weeks following an ischemic stroke, a cerebral abscess develops within the infarcted tissue.

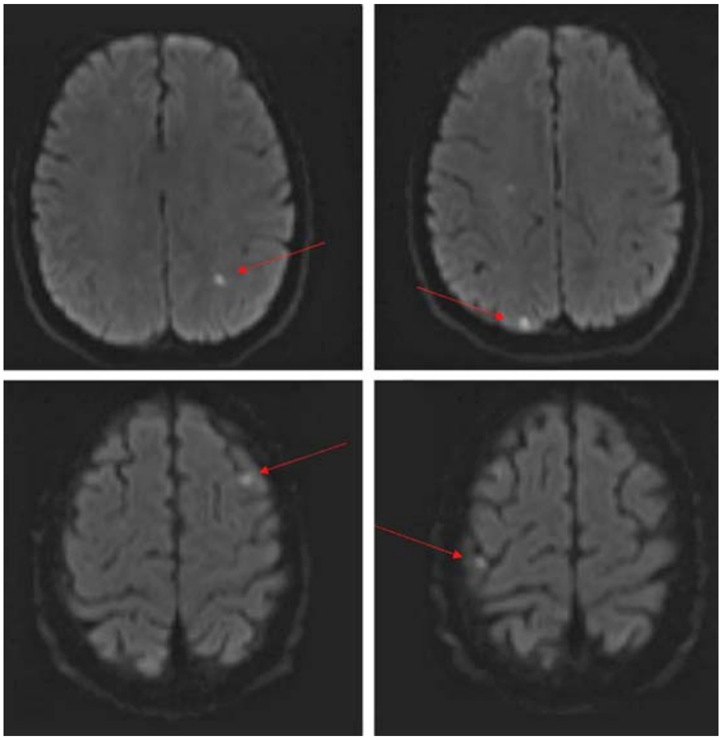

FIGURE 6-5 ■ This 36-year-old man presented with fever and headache and was found to have aortic valve enterococcal endocarditis. These diffusion-weighted MRI sequences illustrate the prototypical small, often asymptomatic embolic ischemic strokes that can occur with left-sided endocarditis.

As with ischemic stroke, intracerebral hemorrhage usually presents with focal neurologic disturbances, but nonlocalizing symptoms, such as headache and decreased level of consciousness, may also predominate. Seizures may occur at the onset of the hemorrhage or later in its course. When subarachnoid hemorrhage occurs, either from rupture of an arteritic vessel or from a mycotic aneurysm, meningismus may be a prominent feature. Headaches may be more diffuse and subacute than is typical with ruptured saccular aneurysms.

Seizures

Although seizures may occur in patients with IE from toxic or metabolic disturbances (e.g., hypoxia, antibiotic toxicity), most often seizures are secondary to ischemic or hemorrhagic stroke. A United States nationwide administrative data-based study of endocarditis hospitalizations from 1998 to 2009 reported 3.8 percent of all cases experienced seizures during the hospitalization, likely an underestimate of clinical seizure frequency.[1] Seizures that are secondary to stroke are usually focal in nature, with or without secondary generalization, whereas seizures due to metabolic or toxic factors are more often primarily generalized. The development of seizures during antibiotic treatment may signify clinical worsening from recurrent stroke, hemorrhagic transformation, or abscess formation. Therefore, the new onset of seizures in a patient with IE should always prompt an urgent neuroimaging study. Rarely, seizures are secondary to antibiotic therapy, with imipenem and fourth-generation cephalosporins most frequently associated with seizures.

Evaluation of Patients

Brain Imaging

All patients with acute focal neurologic deficits should undergo either a noncontrast computed tomography (CT) scan of the head or brain magnetic resonance imaging (MRI). Noncontrast CT may be done more quickly than MRI and is most useful for acutely ruling out hemorrhage or mass effect. If IE is known or suspected, head CT with and without contrast may have additional benefit as areas of increased contrast enhancement allow possible cerebral abscesses or mycotic aneurysms to be distinguished from areas of ischemia. However, brain MRI is the most sensitive modality for detecting the multiplicity of neurologic lesions seen in IE, especially small, multiple emboli (Figs. 6-2 and 6-5).[7] MRI findings have been categorized into four patterns: (1) embolic infarction; (2) multiple patchy infarctions (nonenhancing); (3) small nodular or ring-enhancing white matter lesions (probably microabscesses); and (4) hemorrhagic infarctions (intracerebral or subarachnoid). Multiple cerebral microbleeds, detected best on MRI, occur in up to 60 percent of patients and have also been described as a feature strongly associated with the presence of IE.[9] Hemorrhagic transformation of ischemic infarcts is most often patchy and may follow the contour of the gyri but may also appear as a homogeneous hematoma within an infarct (Fig. 6-3). A clue to the presence of an underlying mycotic aneurysm may be a focal area of cortical enhancement adjacent to an area of hemorrhage.

Vascular Imaging

Based on evidence that subarachnoid hemorrhage can occur without preceding symptoms in more than 50 percent of patients with mycotic aneurysm, some have advocated that all patients with IE should undergo noninvasive vascular imaging with MR angiography (MRA) or CT angiography (CTA) for aneurysm screening. Guidelines suggest screening for mycotic aneurysms in patients with endocarditis and neurologic deficits, including severe headache, erythrocytes or xanthochromia in the CSF, confusion, seizure, or focal neurologic signs.[9,10]

Patients with intracranial hemorrhage are more likely to have mycotic aneurysms than patients with ischemic stroke (22% vs. 1% in one series).[13] Although mycotic aneurysms tend to be small and—unlike saccular aneurysms—occur distally rather than at more proximal arterial branch points, CTA is emerging as a reasonable choice for initial screening, with one series demonstrating that 26 of 81 patients screened with CTA had a mycotic aneurysm, and angiographic findings changed the treatment plan in 21 of these patients.[6]

Patients with ischemic or hemorrhagic stroke who require long-term anticoagulation for mechanical valves or treatment of systemic thromboembolism may also benefit from repeat noninvasive angiography to exclude a mycotic aneurysm, even if initial studies performed at the time of presentation are negative. Patients with known mycotic aneurysms require serial monitoring of aneurysm size to ensure adequate response to therapy; CTA and MRA are likely adequate for this purpose.

Cerebrospinal Fluid Examination

CSF examination was once part of the standard evaluation of patients with IE and neurologic symptoms, but it does not often change management decisions for patients today. The interpretation of CSF findings in IE with acute stroke is complicated by the tendency for patients with stroke unrelated to endocarditis also to have mild to moderate increases in CSF white blood cells, red blood cells, or protein concentration. For these reasons, CSF examination does not usually aid in the diagnosis or management of patients with neurologic symptoms and IE.

Echocardiography

The diagnosis of IE depends on the documentation of a responsible organism on serial blood cultures and, in part, on the presence of valvular abnormalities on echocardiography. Echocardiography is also important in assessing valvular function and excluding conditions such as valve thrombosis or abscess formation that would change clinical management. TEE is more sensitive to mitral and aortic valve pathology and has been reported to change patient management in as many as one-third of cases. Most guidelines recommend TTE as the initial screening study because it can typically be obtained more quickly, but also recommend that TEE be performed to rule out other local cardiac complications.[9,10] Whether serial echocardiography provides data that reliably predict the risk of subsequent stroke or otherwise influence neurologic management is not known.

TREATMENT OF ISCHEMIC STROKE

Antibiotic Therapy

The cornerstone of treatment of IE is appropriate antibiotic therapy directed at the infecting organism. Numerous studies have shown that the risk of either initial or recurrent thromboembolism decreases sharply after the first few days of adequate antibiotic therapy, with one study of almost 1,500 patients demonstrating a risk of 4 percent after the second week of antibiotic therapy.[5] It is therefore critical to ensure that antibiotics are begun promptly and empirically, immediately after drawing initial blood for cultures (preferably three sets from separate sites) in febrile patients with stroke in whom IE is being considered. As effective long-term antimicrobial therapy will be required, the isolation and susceptibility testing of the pathogen are of critical importance. Involvement of a specialist in infectious diseases is recommended, as host defense is essentially ineffective in endocarditis; thus bactericidal antibiotics are more effective than bacteriostatic antibiotics.[9] IE related to infections of implantable cardiac devices is increasing.[1] In this setting, device removal is also typically required in addition to antibiotic therapy. Thorough discussion of a current approach to diagnosis and antimicrobial treatment in various clinical scenarios can be found in the American and European guideline statements, including the appropriate conditions for which antibiotic prophylaxis for the prevention of IE should be considered.[9,10]

Thrombolysis

Acute use of tissue plasminogen activator in patients with ischemic stroke and IE is generally felt to be inadvisable due to an increased bleeding risk. Although there are no large cohort studies, a case series and systematic review that included 40 published cases found a significantly higher post-treatment intracerebral hemorrhage rate among those treated with thrombolysis compared to those treated with endovascular therapy (63% vs. 18%).[14] This report found similar rates of good outcome and mortality in those treated with endovascular treatment, suggesting that clot retrieval may be emerging as the preferred therapy for patients with IE and acute, clinically severe cerebral embolism.

Antiplatelet and Anticoagulant Therapy

The use of antithrombotic therapy (antiplatelet and anticoagulant medication) is controversial in patients with IE, and guidelines recommend these management decisions be made in the setting of a multidisciplinary team.[9,10] Although some studies have suggested that antiplatelet therapy may reduce vegetation size and embolic events, both the European Society of Cardiology and the American Heart Association/American College of Cardiology guidelines for management of IE conclude that data do not support routine initiation of antiplatelet medications, and recommend interruption of antiplatelet therapy if the patient has major bleeding.[9,10]

Anticoagulation in patients with IE remains a controversial and complicated topic. Hemorrhagic complications are clearly more common in anticoagulated patients, but patients with mechanical prosthetic valves may require long-term anticoagulation, and the decision as to whether and for how long to withhold anticoagulants in these patients is complex, depending on the type of valve involved.

ANTICOAGULATION IN NATIVE VALVE ENDOCARDITIS

There is an increased risk of hemorrhagic complications in patients with native valve endocarditis and ischemic stroke who are treated with anticoagulation, and the risk of recurrent embolism is low in those patients receiving appropriate antibiotic therapy. Accordingly, there appears to be no benefit for stroke risk reduction to routinely anticoagulate these patients. An important consideration is whether, prior to the development of endocarditis, these patients were being anticoagulated for a specific indication such as clotting disorders, atrial fibrillation, or pulmonary embolism. In these cases, a review of MRI sequences, looking for occult hemorrhage and vascular lesions, should be part of a risk-to-benefit analysis before anticoagulants are stopped. When anticoagulation is deemed to be necessary, switching from oral to intravenous medications is recommended for optimal control of anticoagulation.[9,10] Whether lower-level anticoagulation (e.g., for prevention of deep venous thrombosis) is safe in patients with stroke and IE is unknown. Because other strategies, such as the use of sequential compression devices, may be equally efficacious, a conservative approach is to use these nonpharmacologic methods primarily.

ANTICOAGULATION IN PROSTHETIC VALVE ENDOCARDITIS

Patients with bioprosthetic valves typically do not receive long-term anticoagulant therapy, thus the same approach as outlined for native valve endocarditis is recommended. Patients with mechanical valve endocarditis and stroke, however, present more difficult management dilemmas.

If a patient with a mechanical valve is receiving long-term anticoagulant therapy and develops a cerebral embolus as a complication of IE, the decision as to whether to continue anticoagulation or temporarily withhold it depends on several factors. Because larger ischemic strokes, especially those secondary to emboli, may be more likely to develop secondary hemorrhagic complications, some authors favor temporarily withholding anticoagulation for several days up to 2 weeks, especially when *S. aureus* is the infecting organism. In general, recommendations favor reinstituting anticoagulation as quickly as possible after the ischemic stroke and following multidisciplinary discussion.[9,10] Patients with intracerebral or subarachnoid hemorrhage and a mechanical valve represent an extremely complex situation in which individual patient clinical, infectious, and valve characteristics must be weighed. In general, anticoagulation is withheld for some period of time and, when reinstated, use of unfractionated or low-molecular-weight heparin is recommended.[9,10] In this situation, determination of the type of mechanical valve and consultation with a multidisciplinary team concerning the risk of valve thrombosis will help guide the decision.

Surgical Treatment

Valve replacement is not recommended therapy for preventing initial or recurrent stroke. Typically, surgery is recommended for patients with severe or refractory congestive heart failure, perivalvular abscess, unstable valve prosthesis, recurrent embolism, infection with a pathogen resistant to effective antimicrobial agents, persistent vegetations greater than 10 mm, or an inability to clear the infection.[9,10] If surgery is required, the timing of the procedure in the setting of stroke is controversial and typically decided on a case-by-case basis. In ischemic stroke, recent cohort studies have suggested that early surgery (within 1 week) is not associated with increased mortality at 6 months or 1 year compared to delayed surgery (greater than 2 weeks). The 2015 American Heart Association guidelines provide multiple recommendations for when early surgery may be considered, including for patients with recurrent emboli.[10] Several risk scores, including the Society of Thoracic Surgeons and De Feo scores, have been developed and may be useful to help identify appropriate surgical candidates.[9,10]

TREATMENT OF HEMORRHAGIC STROKE

Intraparenchymal Hemorrhage

The mainstay of treatment for either primary or secondary intracerebral hemorrhage in patients with IE is the same as that for cerebral emboli: effective treatment of the underlying infectious organism. This is especially true for patients with pyogenic arteritis but is also critical for the treatment of mycotic aneurysms. Some patients with intracerebral hemorrhage and progressive neurologic deterioration, either from expanding hematoma or from edema, may benefit from surgical evacuation of the clot, but no firm guidelines exist. Patients with mechanical valves often will have their anticoagulant discontinued temporarily or converted to an intravenous form as noted earlier. All patients with IE and hemorrhage should have close neurologic monitoring in an intensive care setting since deterioration from recurrent hemorrhage or edema is not uncommon.

Mycotic Aneurysms

The natural history of mycotic aneurysms appears to be that approximately one-third resolve completely with 6 to 8 weeks of antibiotic treatment. The remaining two-thirds are relatively equally divided into those that increase, decrease, or are unchanged.[8] Because of their propensity to resolve with antibiotic therapy, the evaluation and treatment of mycotic aneurysms is highly individualized. Aspects of care that remain unclear are the choice of imaging technique, what frequency of serial angiography is necessary to follow mycotic aneurysms, and the indications and methods of treatment. These complex considerations and a suggested clinical management algorithm are detailed in the 2016 AHA Scientific Statement on mycotic aneurysms and other vascular infections.[8] In general, if an aneurysm enlarges, surgical treatment to prevent rupture is suggested. The need for ongoing or subsequent long-term anticoagulation is another factor that may suggest the need for angiographic surveillance and surgical treatment. Since mycotic aneurysms may persist after adequate antibiotic treatment and since new aneurysms can appear, it is reasonable to repeat angiography, typically with noninvasive techniques, at the conclusion of antibiotic therapy (usually 4 to 6 weeks). Late hemorrhage from a ruptured mycotic aneurysm in patients who have completed adequate antibiotic therapy is rare, therefore continued surveillance of a stable aneurysm following antibiotic treatment is probably unnecessary.

Once an aneurysm is discovered, controversy also exists regarding treatment. Asymptomatic aneurysms are often treated medically, with surgical intervention reserved for those that enlarge or have leaked.[8] Although symptomatic aneurysms may also resolve with antibiotic treatment, most authors favor surgical treatment of any ruptured mycotic aneurysm in addition to antibiotic therapy. This recommendation is usually based on the risk of recurrent bleeding and the need for subsequent cardiovascular surgery or anticoagulation. Aneurysm accessibility and number are other features that influence the decision for surgical treatment. Single aneurysms in a peripheral location are more likely to be treated surgically, with those in more eloquent areas treated with endovascular therapy.[8]

CEREBRAL INFECTION

Cerebral infection, most commonly abscess or meningitis, occurs in less than 10 percent of patients with endocarditis and neurologic complications (Table 6-1). These infections most typically occur after cerebral embolism. Infection arising without clinical evidence of prior embolization is unusual. Encephalitis has also been reported, although the usual pathology in these cases is multiple emboli with microabscess formation.

Meningitis accounts for approximately 5 percent of all neurologic manifestations of IE and is more common with either *S. aureus* or *Streptococcus pneumoniae* infections. When meningitis is associated with involvement of the cerebral cortex, evidenced by gyral enhancement on MRI, the terms “cerebritis” and “meningoencephalitis” are used. Rarely, cerebritis leads to the development of a parameningeal abscess in the cerebral cortex. Meningitis typically results from septic emboli to the meningeal vessels with subsequent CSF colonization. Less commonly, meningitis is nonseptic, resulting from sterile inflammation of the meninges due to blood products or circulating immune complexes released into the CSF.

Cerebral abscesses are rare, with small “microabscesses,” often defined as abscesses smaller than 1 cm, being more common than “macroabscesses.” Cerebral abscesses usually develop as the result of septic emboli and are not necessarily preceded by clinical symptoms. Radiographically, infarction-related abscesses are usually small and multiple and may demonstrate areas of nodular or ring-like enhancement (see Fig. 6-2).

Clinical Presentation

Although the clinical diagnosis of meningitis is infrequent in IE, symptoms of meningitis, including meningismus, headache, encephalopathy, cranial neuropathies, seizures, and increased intracranial pressure may occur. These symptoms may be subtle, especially in the elderly, and when associated with fever, elevated peripheral white blood cell count, and regurgitant murmur should prompt an urgent evaluation for IE.

Evaluation

All patients with known or suspected IE and neurologic symptoms, whether focal or nonfocal, should undergo imaging with noncontrast head CT prior to lumbar puncture because multiple embolic strokes, intracerebral hemorrhage, and abscess may all cause significant compartmental increases in intracranial pressure, thus increasing the risk of cerebral herniation. Lumbar puncture should not be performed in any patient with a focal lesion and evidence of mass effect on neuroimaging studies. Because patients with endocarditis have a propensity toward hematologic abnormalities, coagulation tests and a platelet count are important prior to lumbar puncture. In general, lumbar puncture is infrequently performed if the organism is known and the patient is stable, as CSF findings are unlikely to change antibiotic therapy.

Treatment of Cerebral Infection

As for any type of CNS infection, the goal of treatment is adequate antibiotic therapy to which the infecting organism is sensitive with good CSF penetration. Both microabscesses and macroabscesses usually respond to antibiotic treatment, although macroabscesses may occasionally produce significant mass effect and thus require stereotactic aspiration or surgical drainage.

OTHER NEUROLOGIC COMPLICATIONS

Other extracerebral neurologic complications may rarely occur. Although cerebral and systemic emboli appear to occur with similar frequency, cerebral neurologic complications predominate clinically over extracerebral neurologic complications, probably because the brain receives more blood flow than peripheral neurologic tissues and because cerebral complications are more likely to be symptomatic. Mononeuropathy or mononeuritis multiplex has been reported in patients with IE, and both peripheral and cranial nerves may be involved. Discitis or spondylitis, occasionally with associated epidural abscess or osteomyelitis, may be more common with *S. aureus* infection. Other rare sites of embolization include the spinal cord itself and the retina.

SUGGESTED MANAGEMENT ALGORITHM

The management of neurologic complications of IE is not standardized and substantial variations in care may be necessary based on individual patient characteristics. Nonetheless, it is helpful to consider a treatment algorithm that includes pathways for the major neurologic manifestations of the disease (Fig. 6-6). The two keys to managing patients, regardless of neurologic complications, are: (1) a high level of suspicion of the possibility of IE and (2) prompt initiation of appropriate antibiotic therapy after obtaining multiple sets of blood cultures.

PROGNOSIS

Overall, patients with IE have high mortality, with short-term mortality estimated at 20 percent and long-term mortality at 37 percent based on a meta-analysis of 25 observational studies and 22,382 patients.[15] Among patients with IE, short-term mortality is increased in those with neurologic complications compared to those without them.[2,4,16] Mortality is higher in infections with more virulent organisms, with some studies showing an association between *S. aureus* infection and mortality, and others reporting increased mortality as vegetation size increases.[9,10,12] Intracerebral hemorrhage appears to confer added risk, with reported mortality of 40 to 90 percent. Although rare, rupture of a mycotic aneurysm is associated with even higher mortality.

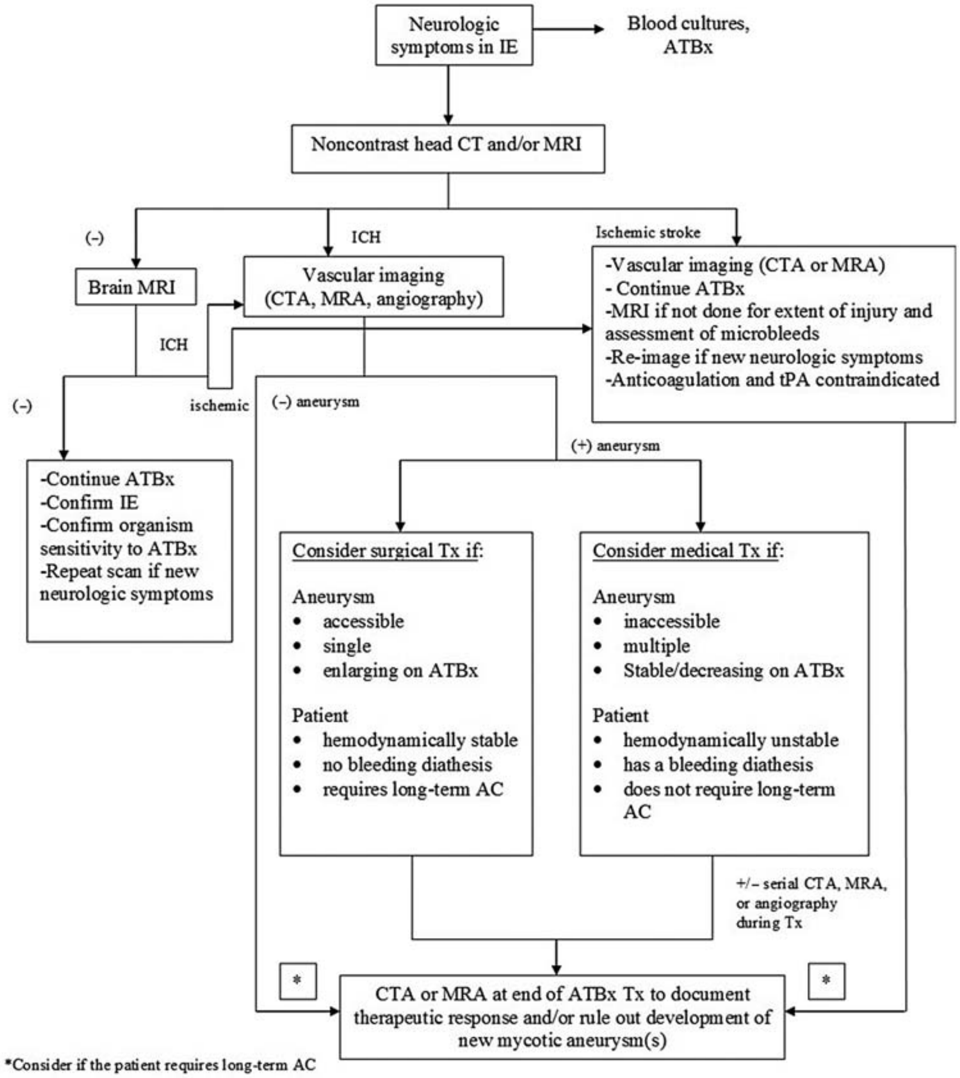
Neurologic symptoms in IE
Blood cultures, ATBx
Noncontrast head CT and/or MRI
(-)
ICH
Ischemic stroke
Brain MRI
Vascular imaging (CTA, MRA, angiography)
-Vascular imaging (CTA or MRA)
- Continue ATBx
-MRI if not done for extent of injury and assessment of microbleeds
-Re-image if new neurologic symptoms
-Anticoagulation and tPA contraindicated
ICH
(-)
ischemic
(–) aneurysm
(+) aneurysm
-Continue ATBx
-Confirm IE
-Confirm organism sensitivity to ATBx
-Repeat scan if new neurologic symptoms
Consider surgical Tx if:
Aneurysm
• accessible
• single
• enlarging on ATBx
Patient
• hemodynamically stable
• no bleeding diathesis
• requires long-term AC
Consider medical Tx if:
Aneurysm
• inaccessible
• multiple
• Stable/decreasing on ATBx
Patient
• hemodynamically unstable
• has a bleeding diathesis
• does not require long-term AC
+/– serial CTA, MRA, or angiography during Tx
*
*
CTA or MRA at end of ATBx Tx to document therapeutic response and/or rule out development of new mycotic aneurysm(s)
*Consider if the patient requires long-term AC

FIGURE 6-6 ■ Suggested management algorithm for patients with focal neurologic deficits and known or suspected IE. Factors favoring either surgical or medical treatment of mycotic aneurysms are presented, but management of these cases is highly individualized. Repeat angiography at the conclusion of medical therapy is suggested for all patients with known mycotic aneurysms and may be considered either for patients with intracerebral hemorrhage and a negative initial angiogram or for patients with ischemic stroke who require long-term anticoagulation. ATBx, antibiotics; CTA, Computed tomography angiography; ICH, intracerebral hemorrhage; LP, lumbar puncture; MRA, magnetic resonance angiography; Tx, treatment.

Longer-term mortality following IE may be less related to neurologic events, although some studies do find an association between neurologic complications and 1-year mortality.[16] Other studies suggest that age and other medical comorbidities including cancer, renal disease, and heart failure are more associated with mortality at 1 year.[3,4] The risk of recurrent neurologic events, either embolic or hemorrhagic, is low, with one study reporting 9 percent of patients having recurrent emboli (either cerebral or systemic).[5] Elimination of recurrent events appears to depend more on effective antibiotic treatment than on any other specific therapy.

CONCLUDING COMMENTS

Although IE has evolved somewhat with regard to prevalence, site, and susceptibility of infecting organisms, the proportion of patients with neurologic manifestations and the type of neurologic complications remain remarkably consistent. Most neurologic complications are caused by embolization of friable valvular material resulting in either ischemic or hemorrhagic stroke. A high index of suspicion for IE as the cause of stroke is critical, and some of the common treatments for acute stroke, such as thrombolysis, are often contraindicated in patients with IE and ischemic stroke. Although many clinical decisions in patients with neurologic manifestations of IE must be individualized, it is clear that the cornerstone of prevention and treatment of all neurologic complications is rapid delivery of appropriate antibiotic therapy.

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CHAPTER

7

Neurologic Complications of Hypertension

ANTHONY S. KIM

EPIDEMIOLOGY
PATHOPHYSIOLOGY
EVALUATION AND TREATMENT
STROKE
CEREBRAL ANEURYSMS
  Unruptured Cerebral Aneurysms
  Subarachnoid Hemorrhage
INTRACEREBRAL HEMORRHAGE
LACUNAR INFARCT
PERIVENTRICULAR WHITE MATTER DISEASE
CEREBRAL AUTOSOMAL-DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY
CAROTID ARTERY STENOSIS
INTRACRANIAL ATHEROSCLEROSIS
AORTIC ARCH ATHEROSCLEROSIS
CARDIAC EMBOLUS
DEMENTIA
HYPERTENSIVE ENCEPHALOPATHY
ECLAMPSIA
IMMUNOSUPPRESSION

Blood pressure was first measured in 1707 by an English divinity student, Stephan Hales, using a glass tube attached directly into the arteries of animals. Methods of measurement improved slowly over the next 200 years, with Nikolai Korotkoff describing the modern cuff-and-stethoscope technique in 1905. At the turn of the twentieth century, Theodore Janeway recognized that hypertension was an indicator of poor prognosis, including mortality from stroke in the years that followed the development of hypertension. A tolerable oral agent to treat hypertension was not available until 1957, when chlorothiazide was shown to reduce blood pressure in patients with essential hypertension.

Both acute hypertension and chronic hypertension produce neurologic disease. Acute hypertension is associated with hypertensive encephalopathy, a relatively uncommon presentation since the widespread identification and treatment of hypertension. Chronic hypertension is associated with stroke, which is its most important neurologic complication. All stroke subtypes are linked to hypertension, including ischemic infarction, intraparenchymal hemorrhage, and aneurysmal subarachnoid hemorrhage. Chronic hypertension is also associated with dementia.

EPIDEMIOLOGY

Both systolic and diastolic blood pressures are distributed approximately normally in the population. For convenience, physicians have defined pathologic states such as hypertension based on specific blood pressure thresholds. Most recently, hypertension has been defined as a systolic blood pressure >130 mmHg or diastolic >80 mmHg. Thus defined, hypertension is common, affecting approximately 116 million adults in the United States in 2016; its prevalence is projected to increase by 60 percent and affect 1.54 billion adults worldwide by 2025.[1,2]

Despite the frequent division of blood pressure into diagnostic categories such as hypertension and

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normotension, there is no obvious threshold at which higher blood pressure begins affecting the risk of complications, and even patients with diastolic blood pressures of 80 to 90 mmHg are at increased risk of stroke compared with those with blood pressures of 70 to 80 mmHg (Fig. 7-1). Reflecting an awareness of the continuous risk associated with blood pressure, normal blood pressure has been defined as a systolic <120 mmHg and diastolic <80 mmHg and blood pressures of 120 to 129 mmHg systolic and <80 mmHg diastolic have been termed "elevated blood pressure."[3]

Related to the concept of thresholds for defining hypertension and normotension is the question of what the optimal blood pressure targets for treatment should be. The recent Systolic Blood Pressure Intervention Trial (SPRINT) was terminated early after demonstrating fewer cardiovascular events with an intensive blood pressure target (systolic blood pressure <120 mmHg) compared to a standard blood pressure target (systolic <140 mmHg).[4] Note that patients with a history of stroke (or diabetes) were specifically *excluded* from this study, and hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure were more common with intensive treatment. Also, the automated oscillometric blood pressure measurements used in the study are 5 to 10 mmHg lower than routine clinic measurements. How well these results obtained in a population of patients with higher cardiovascular risk generalize to patients with neurologic diseases, frailty, or a history of stroke or cerebrovascular diseases is uncertain.

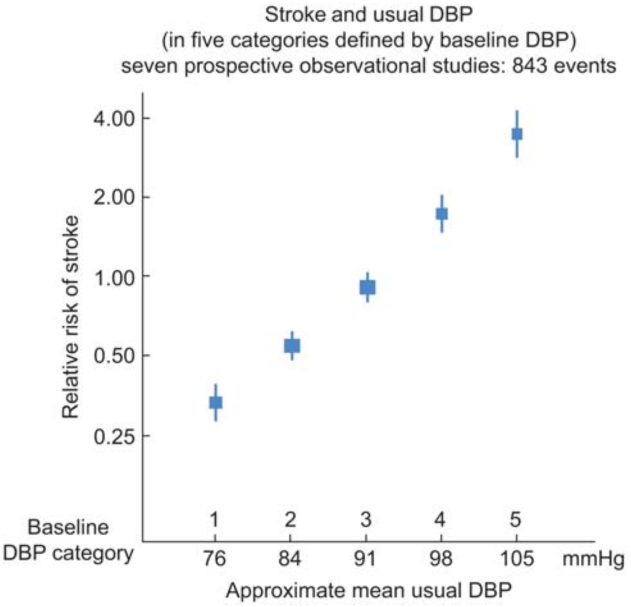

FIGURE 7-1 ■ Relative risks of stroke. Estimates of the usual diastolic blood pressure (DBP) in each baseline DBP category are taken from mean DBP values 4 years after baseline in the Framingham study. Solid squares represent disease risks in each category relative to risk in the whole study population; sizes of squares are proportional to the number of events in each DBP category; and 95 percent confidence intervals for estimates of relative risk are denoted by vertical lines. (Reprinted with permission from MacMahon S, Peto R, Cutler J, et al: Blood pressure, stroke, and coronary heart disease. Lancet 335:764, 1990.)

PATHOPHYSIOLOGY

In the brain, the primary pathophysiologic process of hypertension is related to increases in vasomotor tone and peripheral arterial resistance. Acute elevation in blood pressure results in constriction of small arteries in the brain in a compensatory response termed *autoregulation*, leading to blood flow to the brain being maintained at a relatively constant level over a range of pressures. At high pressures, vasoconstriction is thought to be protective by reducing pressure at smaller, more distal vessels. Acute severe hypertension overwhelms normal autoregulation at a mean arterial pressure of approximately 150 mmHg, with increased cerebral blood flow occurring above this pressure threshold. Vasoconstriction in acute hypertension is patchy, and some small vessels are exposed to high pressures, which may lead to endothelial injury and focal breakdown of the blood–brain barrier. Acute hypertensive encephalopathy is a fulminant presentation of this process. Fibrinoid necrosis of small vessels may also occur, lowering the threshold for future ischemic and hemorrhagic events.

Chronic hypertension results in cerebral vascular remodeling. The media hypertrophies, and the lumen becomes narrowed. These changes are protective, with reduction in wall tension and shifting of the autoregulation curve to allow compensation at higher blood pressures. However, vascular remodeling is accompanied by endothelial dysfunction, with impaired relaxation and poor compensation for hypoperfusion. The result is greater susceptibility to ischemic injury due to reduced collateral flow.

Hypertension also predisposes to atherosclerosis. Hypertension is proinflammatory and is accompanied by increased plasma oxygen free radicals. Free radicals induce vascular smooth muscle cell proliferation and may oxidize low-density lipoproteins, which in turn promotes macrophage activation and monocyte extravasation. Angiotensin II is elevated in many hypertensive patients and may play a direct role in atherogenesis independent of its effects on blood pressure. It directly stimulates smooth muscle cell growth, hypertrophy, and lipoxygenase activity, with resultant inflammation and low-density lipoprotein oxidation, thus accelerating atherosclerosis.

EVALUATION AND TREATMENT

The gold standard of blood pressure measurement has been auscultation using a mercury sphygmomanometer with the patient in the seated position after a 5-minute rest and with the patient's feet resting on the floor and the arm supported at heart level during the measurement. Accurate readings depend on the use of an appropriate-sized cuff with the bladder covering at least 80 percent of the arm. The classification of blood pressure into specific diagnostic categories had been based on the average of two or more readings on each of two or more office visits.

However, automated oscillometric blood pressure devices are common in the clinic and the home, and ambulatory devices that measure blood pressure at frequent intervals over the course of the day and night during normal activities are also available. Since these devices can take multiple consecutive readings and measurements can be made unattended or at home to reduce the white coat effect, data from clinic and out-of-office readings can be integrated to formally establish the diagnosis of hypertension as well. Different methods of blood pressure measurement may yield results that are systematically different, so careful attention to the specific method used to measure blood pressure when interpreting the results of recent clinical trials is vital.

A complete history and physical examination with basic laboratory measurements are essential to evaluate for identifiable causes of hypertension and assess risk. Several patient characteristics may suggest an identifiable cause of hypertension including young age, severe hypertension, hypertension that is refractory to multiple interventions, and physical or laboratory findings suggestive of endocrinologic disorders, such as truncal obesity or hypokalemia. Abdominal bruits or decreased femoral pulses may also be an indicator of renovascular disease or coarctation of the aorta. Discrepant readings between each arm raise the concern for subclavian stenosis and peripheral arterial disease.

Lifestyle modification is recommended as an initial therapy for patients with blood pressure of 120/80 mmHg or higher. Effective lifestyle interventions include weight loss, limiting alcohol intake, aerobic physical activity, adequate potassium intake, dietary salt restriction, and comprehensive dietary regimens such as the Dietary Approaches to Stop Hypertension (DASH) eating plan. The addition of pharmacologic treatment with one or more antihypertensives is justified when baseline atherosclerotic cardiovascular risk is high such as with established cardiovascular disease or stroke, diabetes, chronic kidney disease, or advanced age (>65) and when blood pressure readings at initial presentation are particularly high.

The reductions in cardiovascular risk that result from pharmacologic treatment of blood pressure have more to do with the degree of blood pressure reduction achieved than the particular antihypertensive agent used. Monotherapy with thiazides or related diuretics, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) is reasonable subject to certain considerations for defined subpopulations (e.g., ACE-inhibitor or ARB with chronic kidney disease) and an individual patient's experience with tolerability and side effects. For patients with blood pressure that is well above goal at initial presentation, starting two first-line agents may be warranted from the outset, though regardless of the initial approach, a systematic approach to dose escalation and combination therapy is essential to achieve adequate blood pressure control as evidenced by the results of comprehensive hypertension management programs.[5]

There are many benefits to treating hypertension, including a reduction in myocardial infarction, congestive heart failure, retinopathy, renal failure, and overall mortality. The focus of the remainder of this chapter is on specific neurologic complications of hypertension and the unique aspects of treatment that they necessitate.

STROKE

Of all the identified modifiable risk factors for stroke, hypertension appears to be the most important, owing to its high prevalence and its strong association with elevated stroke risk. Based on epidemiologic data, approximately 50 percent of strokes could be prevented if hypertension were eliminated (Table 7-1). Studies have shown that even small reductions in blood pressure with active treatment (e.g., a reduction of even 5 mmHg diastolic) can result in large (~40%) reductions in stroke risk. The benefits of blood pressure reduction on stroke risk extend similarly to the elderly with isolated elevations in systolic blood pressure. Studies of patients aged 60 years or more have demonstrated similar reductions in stroke with reductions in systolic blood pressure and the best available data suggest that benefits of treating blood pressure in the oldest old (>85 years) are comparable to those seen in younger individuals.

In much of the developed world, improvements in hypertension awareness, increased use of antihypertensive medications, and better blood pressure control at a population level have largely paralleled a steady decline in the age-adjusted burden of disease from stroke. However, on a global scale, hypertension remains the leading risk factor for death worldwide and the developing world continues to bear a disproportionate, substantial, and increasing burden of disease from stroke (Fig. 7-2).

Hypertension contributes to each of the major intermediate causes of both ischemic and hemorrhagic stroke including carotid stenosis, intracranial atherosclerosis, small-vessel arteriosclerosis, and the development of both macroscopic and microscopic aneurysms. Each of these conditions is considered separately in this chapter.

In the acute phase of cerebral ischemia, hypertension may play a compensatory role in maintaining cerebral perfusion to viable but threatened areas of the brain. Loss of normal cerebral autoregulation has been demonstrated in areas of ischemic brain. When autoregulation is lost, blood flow to the brain becomes directly proportional to mean arterial pressure and therefore, in theory, pharmacologic increases in blood pressure could have salutatory effects in preserving hypoperfused regions of the brain. In some studies, rapid pharmacologic reductions in blood pressure have predicted worse outcomes, and there are numerous anecdotal reports of the recrudescence of stroke symptoms after a decrease in blood pressure. Therefore, withholding or reducing pharmacologic treatments of blood pressure in acute ischemic stroke seems reasonable unless the blood pressure exceeds 220/120 mmHg or acute end-organ injury or administration of thrombolytics necessitates setting a lower goal.

In the chronic phase, there is overwhelming evidence to support the use of pharmacologic interventions to lower blood pressure for secondary stroke prevention. Studies of combination therapy with ACE-inhibitors and thiazide diuretics in patients with a history of stroke have found greater reductions in the relative risk of recurrent stroke compared to ACE-inhibitors alone, largely owing to greater reductions in blood pressure that are achieved with combination therapy. Although therapy with renin-angiotensin system antagonists and diuretics may provide especially strong benefits for stroke prevention, particularly when compared with β-blockers, once again, the degree of hypertension control that is achieved is usually the best predictor of protection against recurrent stroke. Therefore, response to therapy and other comorbidities, such as heart failure, diabetes, asthma, and arrhythmia, should be considered when deciding on an appropriate antihypertensive drug regimen. Although the acute physiologic response to stroke can induce a

TABLE 7-1 ■ Estimated Impact of Modifiable Risk Factors on Stroke in the United States*

Risk Factor	Percentage Exposed	Relative Risk	Population-Attributable Risk (%)	Projected Number of Strokes Preventable
Hypertension	56	2.7	49	370,000
Cigarette smoking	27	1.5	12	92,000
Atrial fibrillation	4	3.6	9	71,000
Heavy alcohol consumption	7	1.7	5	35,000

*Relative risks are from the Framingham study. Population-attributable risk is the expected decrease in stroke rates if the risk factor were eliminated. Projected number of strokes preventable is based on an estimated 750,000 strokes per year.

Adapted from Gorelick PB: Stroke prevention: an opportunity for efficient utilization of health care resources during the coming decade. Stroke 25:220, 1994.

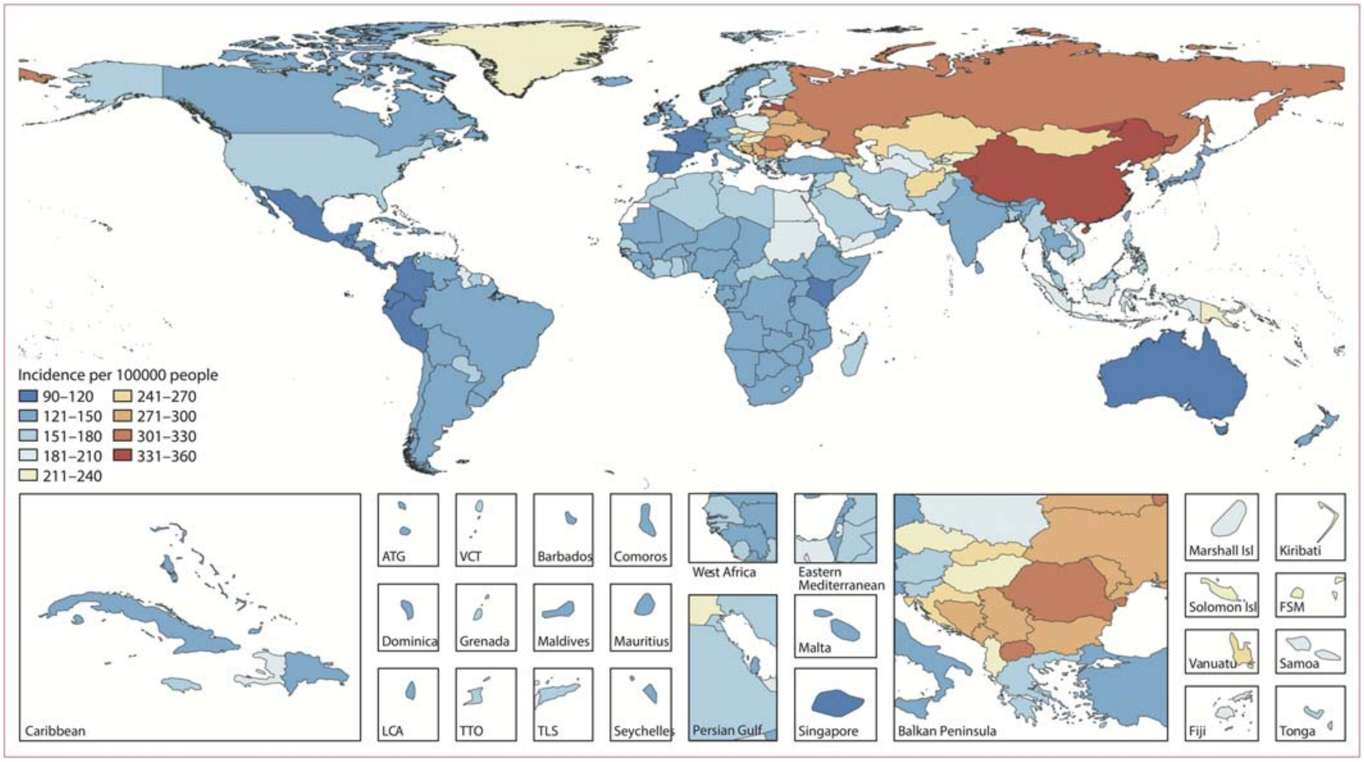
Incidence per 100000 people
90–120
121–150
151–180
181–210
211–240
241–270
271–300
301–330
331–360
Caribbean
ATG
VCT
Barbados
Comoros
West Africa
Eastern Mediterranean
Balkan Peninsula
Marshall Isl
Kiribati
Dominica
Grenada
Maldives
Mauritius
Malta
Solomon Isl
FSM
Vanuatu
Samoa
LCA
TTO
TLS
Seychelles
Persian Gulf
Singapore
Fiji
Tonga

FIGURE 7-2 ■ Age-standardized stroke incidence by country, for both sexes, 2016. (Reprinted with permission from GBD 2016 Stroke Collaborators: Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 18:439, 2019.)

short-term hypertensive reaction that may necessitate a de-escalation of antihypertensive therapy in certain patients, the general approach of initiating antihypertensive therapy before hospital discharge may improve patient adherence and blood pressure control during the crucial transition in care to the outpatient setting and over the longer term.

CEREBRAL ANEURYSMS

Cerebral aneurysms are focal dilatations of blood vessels. Subarachnoid hemorrhage, an important form of hemorrhagic stroke, occurs when a cerebral aneurysm ruptures (Fig. 7-3). Hypertension is associated with cerebral aneurysm formation and with subarachnoid hemorrhage. Hypertension is more commonly listed as a secondary diagnosis in patients admitted with unruptured aneurysms compared to hospitalized patients more generally, and studies suggest that hypertension may confer a nearly threefold higher risk of subarachnoid hemorrhage compared to nonhypertensive controls.

The cause of the development and rupture of cerebral aneurysms is multifactorial. Epidemiologic studies have identified several environmental risk factors for subarachnoid hemorrhage other than hypertension. Cigarette smoking doubles the risk of subarachnoid hemorrhage, perhaps by increasing the release of proteolytic enzymes that affect blood-vessel integrity. Heavy alcohol consumption increases subarachnoid hemorrhage risk perhaps due to alcohol-induced hypertension, relative anticoagulation, or increased cerebral blood flow. Oral contraceptives are associated with a small but significant excess risk of subarachnoid hemorrhage.

Genetic factors are also important to aneurysm formation and subarachnoid hemorrhage. The risk of subarachnoid hemorrhage is much greater in patients with an affected first-degree relative, and the prevalence of unruptured aneurysms is probably at least twice as high when a family history of aneurysm is present. Females are nearly twice as likely as males to have an aneurysm or to present with subarachnoid hemorrhage. African Americans have twice the rate of subarachnoid hemorrhage as whites. Polycystic kidney disease, Ehlers–Danlos syndrome type 4, and α_1-antitrypsin deficiency are also associated with increased risk.

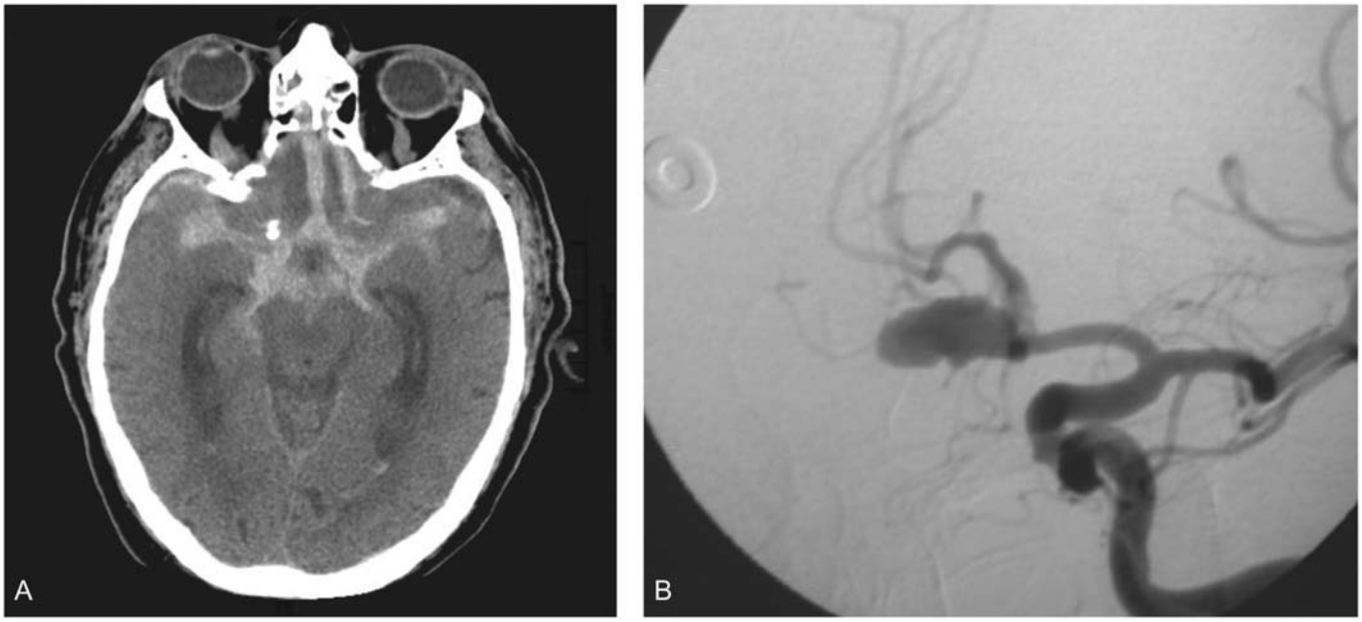

FIGURE 7-3 ■ A ruptured anterior communicating artery aneurysm producing acute subarachnoid hemorrhage. *A*, Head computed tomography (CT) shows a large amount of blood at the base of the brain and a small amount of intraventricular blood. *B*, Angiogram reveals a complex saccular aneurysm.

Unruptured Cerebral Aneurysms

Estimates of the prevalence of unruptured aneurysms vary widely but seem to cluster around an overall prevalence of about 3 percent. The vast majority of aneurysms are less than 10 mm in diameter, and most are less than 6 mm. Cerebral aneurysms are being detected more frequently as imaging technology improves and as imaging studies are used more frequently.

Unruptured aneurysms are often asymptomatic and discovered incidentally in the work-up for an unrelated problem. Some aneurysms produce symptoms by compressing neighboring structures. Presentation with a new cranial neuropathy is considered a worrisome sign of imminent rupture and often prompts urgent treatment. New headaches are also a presenting sign of unruptured aneurysm. Although migraine may simply represent an unrelated occurrence that prompts head imaging, some headaches may be due to the aneurysm itself. A sudden, severe "thunderclap" headache may herald rapid aneurysm growth or a small leak without evidence of overt subarachnoid hemorrhage.

Catheter angiography remains the gold standard for detecting aneurysms and for characterizing the morphology and anatomy of these lesions for planning treatment. Head computed tomography (CT) does not reliably detect unruptured aneurysms, though CT angiography and magnetic resonance (MR) angiography are capable of detecting many aneurysms, particularly those that are larger than 3 mm.

The prognosis of unruptured aneurysms, as reflected in the rate of rupture, is a subject of controversy, although most small aneurysms appear to be at very low risk of rupture. The size of the aneurysm (≥7 mm in maximum diameter) and location at the basilar tip or posterior communicating artery are independent predictors of hemorrhage. For patients with no history of subarachnoid hemorrhage, the annual risk of hemorrhage for small aneurysms (less than 7 mm in diameter) in the anterior circulation is essentially close to 0 percent and about 0.5 percent when the aneurysm is located in the posterior circulation.

The standard of care for treatment of aneurysms had historically been surgical clipping, in which a metal clip is placed over the neck of the aneurysm, thereby isolating it from the circulation. However, coil embolization, which involves packing platinum coils into an aneurysm through a microcatheter with an angiographic endovascular procedure, appears to be a generally safer approach when technically feasible, although coiled aneurysms can sometimes require retreatment in early follow-up.

Whether a given aneurysm requires treatment depends on the anticipated rupture rate and procedural risks. For asymptomatic aneurysms smaller than 7 mm with no history of subarachnoid hemorrhage, treatment may not be justified, particularly when in the anterior circulation, given the risks of surgery or endovascular therapy. Treatment of unruptured aneurysms appears to be cost-effective from a societal perspective when they are larger or symptomatic or when there is a history of subarachnoid hemorrhage from a different aneurysm. Controlling or eliminating risk factors, such as hypertension, smoking, and alcohol abuse, may reduce rupture rates, but this has not been systematically established.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage accounts for approximately 5 percent of all strokes, but it tends to occur at a younger age than other stroke subtypes, with median age at death typically in the 50s to 60s for subarachnoid hemorrhage, as compared to 70s for intracerebral hemorrhage, and 80s for ischemic stroke. Subarachnoid hemorrhage accounts for nearly one-third of the years of potential life lost before age 65 due to stroke. Case fatality rates have been improving, but 10 to 20 percent remain disabled and dependent at follow-up.

Presentation with subarachnoid hemorrhage generally involves the sudden onset of severe headache, sometimes accompanied by neck pain. Alteration of consciousness occurs in a minority of patients, but it may be severe enough to produce coma or sudden death outside the hospital. Head CT often shows blood surrounding the base of the brain. Intraventricular and intraparenchymal hemorrhage may be present and can provide clues as to the location of the ruptured aneurysm. Lumbar puncture may rarely show signs of hemorrhage when there is no evidence of it on head CT. Blood in the spinal fluid that does not clear is suggestive of acute subarachnoid hemorrhage. Xanthochromia is present in nearly all cases and may persist for more than 3 weeks, but its appearance can be delayed by more than 12 hours in 10 percent of cases. Angiography is required to characterize the aneurysm and to plan treatment.

Prognosis depends on the ability to treat the underlying aneurysm and on the patient's condition at presentation. Recurrent hemorrhage occurs in more than 4 percent of untreated patients during the first day and then in 1 to 2 percent per day for the next 2 weeks; re-rupture is associated with even greater fatality and morbidity than primary rupture. Regardless of treatment and recurrent hemorrhage, the level of consciousness at presentation is the major predictor of mortality (Table 7-2). The World Federation of Neurological Surgeons developed a Universal Subarachnoid Hemorrhage Grading Scale, similar to the older Hunt and Hess scale, which has been widely adopted but offers little advantage over determinations based on level of consciousness alone.

To reduce the risk of recurrent hemorrhage, ruptured aneurysms should be identified rapidly and repaired with surgical clipping or endovascular coil embolization as early as feasible. Hydrocephalus from obstruction of the cerebral aqueduct or the meninges by blood clot may require external ventricular drainage. Vasospasm is a common complication

TABLE 7-2 ■ Overall Outcome after Subarachnoid Hemorrhage by Consciousness Level on Admission*

	Good Recovery		Moderately Disabled		Severely Disabled		Vegetative Survival		Dead		Totals	
Consciousness Level	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Alert	1,279	74.3	130	7.5	70	4.1	18	1.0	225	13.1	1,722	100.0
Drowsy	608	53.5	125	11.0	71	6.3	19	1.7	313	27.6	1,136	100.0
Stuporous	105	30.2	48	13.8	28	8.0	15	4.3	152	43.7	348	100.0
Comatose	35	11.1	17	5.4	25	7.9	11	3.5	227	72.1	315	100.0
Totals	2,027	57.6	320	9.1	194	5.5	63	1.8	917	26.0	3,521	100.0

*Percentages are of row totals. Relationship between admission level of consciousness and outcome: $\chi^2 = 720.5$; $P < 0.001$.

From Kassell NF, Torner JC, Haley EC, et al: The International Cooperative Study on the timing of aneurysm surgery. J Neurosurg 73:18, 1990, with permission.

that can produce delayed cerebral ischemia due to blood vessel constriction in areas exposed to subarachnoid blood. It becomes symptomatic in one-third of cases, usually 3 to 14 days after hemorrhage, and can result in cerebral infarction or death. Transcranial Doppler ultrasonography can detect vasospasm before it becomes symptomatic. Oral nimodipine, a calcium-channel antagonist, reduces poor outcomes from vasospasm and is generally given for the first 21 days after the initial bleed. Hypertension induced with pressors and maintaining adequate hydration with intravenous fluids may reduce the risk of infarction, but these measures have never been studied in trials. They should not be used in patients with untreated aneurysms because of the risk of precipitating further episodes of bleeding. Vasodilatation through angioplasty or intra-arterial verapamil can reverse angiographic vasospasm in many cases, but clinical benefits have not been definitely demonstrated.

INTRACEREBRAL HEMORRHAGE

Bleeding directly into the substance of the brain is termed *intraparenchymal* or *intracerebral hemorrhage* (Fig. 7-4). It may occur as a complication of ischemic stroke, termed *hemorrhagic conversion*, or as the primary injury without preceding ischemia. Hypertension is the most important identified risk factor for intracerebral hemorrhage. More than 70 percent of patients with intracerebral hemorrhage have a history of hypertension, and the risk of hemorrhagic stroke increases exponentially as systolic blood pressure increases.

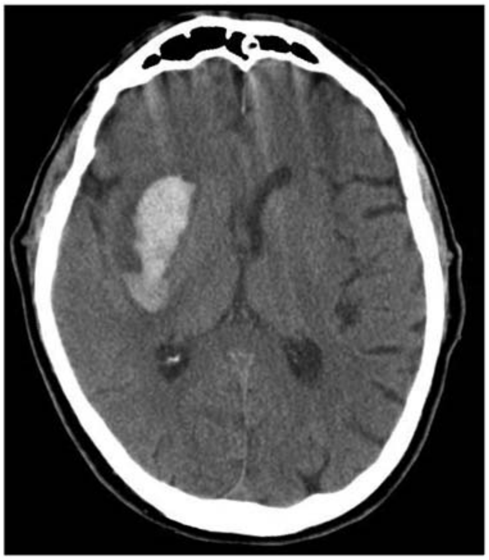

FIGURE 7-4 ■ Head CT of an acute basal ganglia intracerebral hemorrhage with mass effect compressing the ventricles.

Intracranial hemorrhage is responsible for 10 to 15 percent of all stroke deaths but for more than one-third of the years of life lost before age 65 due to the younger age distribution of intracerebral hemorrhage compared with other causes of stroke. Case fatality rates are high, with one-quarter to one-half of patients dead at 1 month and only about one-fifth of patients returning to independence at 6 months.

Other risk factors for intracerebral hemorrhage include age, race, substance abuse, anticoagulation, platelet dysfunction, and vascular and structural anomalies. Rates of intracerebral hemorrhage increase with age. African Americans have higher rates than whites, with larger differences at younger ages. Cocaine and amphetamine use are associated with increased risk, particularly acutely, possibly because of transient severe hypertension. Abnormalities in clotting may account for an increased incidence of intracerebral hemorrhage with heavy alcohol use. Excessive anticoagulation and antiplatelet therapy also increase the risk of intracerebral hemorrhage. Thrombolytic agents used for ischemic stroke and myocardial infarction cause intracerebral hemorrhage in some cases. It may also occur with severe thrombocytopenia and platelet dysfunction.

Intracerebral hemorrhage may result from and occur in brain tumors, such as glioblastoma multiforme and in metastatic melanoma, choriocarcinoma, renal cell carcinoma, and bronchogenic carcinoma. Cerebral amyloid angiopathy, a vasculopathy common in the elderly, is associated with lobar hemorrhages, often centered at the gray—white junction. Other punctate hemorrhages may be apparent on gradient-echo or susceptibility-weighted MR images (Fig. 7-5), supporting the diagnosis. Arteriovenous malformations, abnormal complexes of arteries and veins in brain parenchyma, account for about 5 percent of intracerebral hemorrhages. Cavernous malformations are dense collections of thin-walled vascular channels and appear to be the cause of intracerebral hemorrhage in about 5 percent of autopsies. They are not apparent on angiography but have a "popcorn"

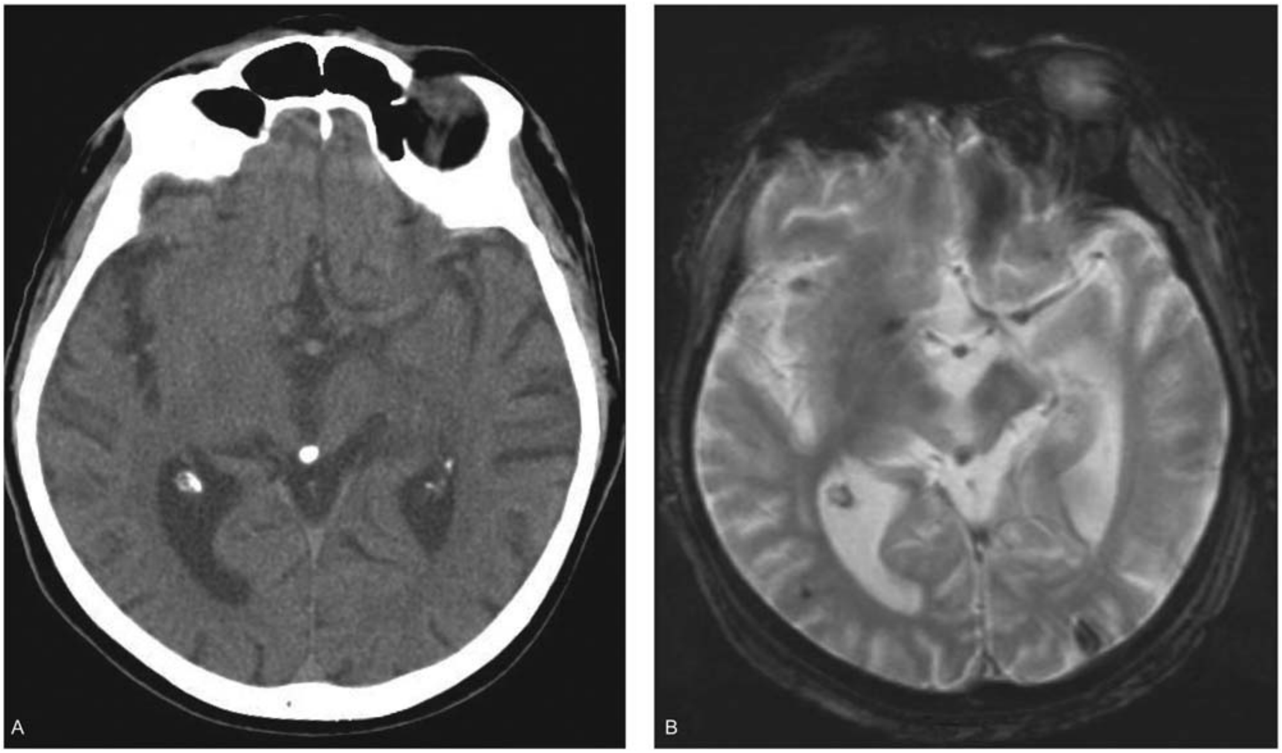

FIGURE 7-5 ■ Imaging findings of amyloid angiopathy, with no evidence of hemorrhage on CT, *A*, but multiple punctate areas of susceptibility at the gray–white junction on T2-weighted multiplanar gradient-recalled (MPGR) magnetic resonance imaging (MRI), *B*, suggesting prior hemorrhage.

appearance on MR images, with a hyperintense core surrounded by hypointense hemosiderin from previous small hemorrhages (Fig. 7-6). Aneurysms may produce intracerebral hemorrhages when blood is directed into the brain, but these rarely are mistaken for primary hypertensive hemorrhages.

Primary hypertensive intracerebral hemorrhage was thought to be caused by chronic vascular injury, resulting in formation of microscopic aneurysms, first characterized by Charcot and Bouchard in 1868. Advances in pathologic tissue preparation have raised doubts about the frequency and importance of microscopic aneurysms, which may actually represent complex vascular coils. More recently, fibrinoid necrosis of small arteries has been proposed as the initial step in intracerebral hemorrhage. Brain injury occurs because of compression of surrounding tissue and from the direct toxic effects of blood. Mass effect from the hematoma may lead to uncal, subfalcine, tonsillar, or transtentorial herniation, depending on location, and death may ensue.

Clinical presentation depends on the location and size of the hemorrhage (Table 7-3). Nearly all intracerebral hemorrhage is characterized by the sudden onset of neurologic deficits, progressing over minutes and accompanied by headache, often with alteration of consciousness. Deterioration due to surrounding edema, hydrocephalus, or continuing or recurrent hemorrhage often occurs within the first 24 hours but may be delayed by days.

Prognosis is multifactorial. Hemorrhage volume, most easily measured by halving the product of the length, width, and depth on axial head CT images, is a powerful predictor of mortality. Mortality is much greater in those with intraventricular extension of blood. Hydrocephalus due to intraventricular extension or cerebrospinal fluid (CSF) outflow obstruction also predicts in-hospital mortality. Lower Glasgow Coma Scale scores at presentation, advanced age, infratentorial location, and initial elevated blood pressure or pulse pressure are other independent predictors of mortality. Simple multivariable prediction models that integrate these factors have been developed and validated.

Urgent head CT is required in patients with suspected intracerebral hemorrhage. MRI is as sensitive as CT for detecting hemorrhage and is more

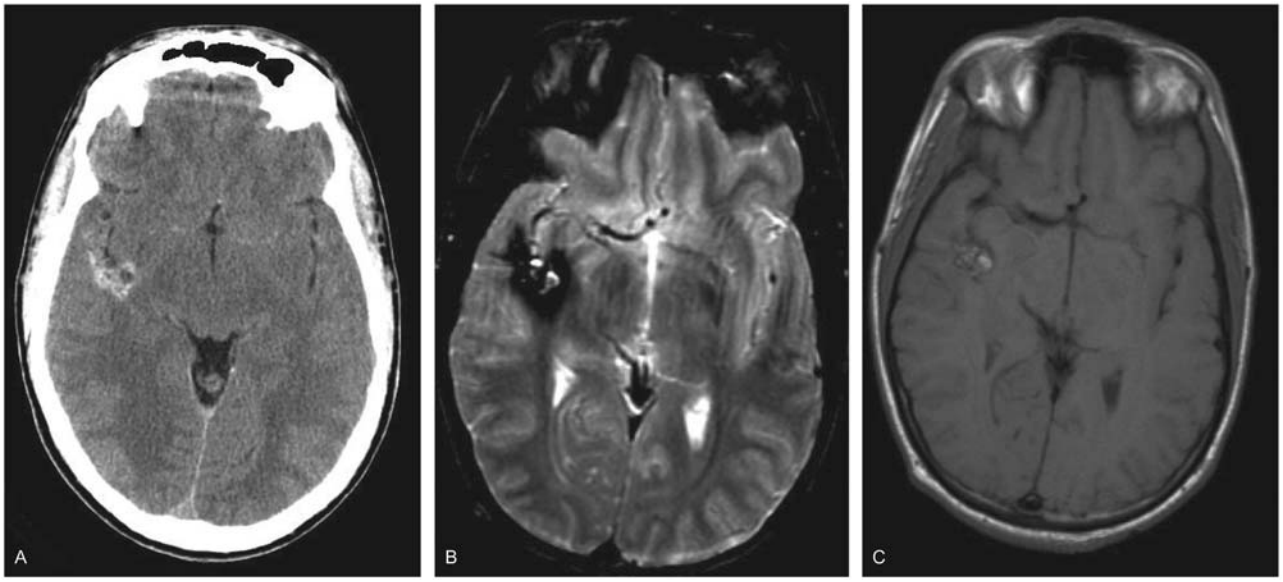

FIGURE 7-6 ■ A cavernous malformation with a small amount of acute, intracerebral hemorrhage surrounding it on head CT, *A*. T2-weighted brain MRI *B*, shows a lesion with a focal area of high signal intensity surrounded by a thick rim of hypointense hemosiderin. T1-weighted brain MRI *C*, showing the typical "popcorn" appearance. The high signal intensity represents methemoglobin.

TABLE 7-3 ■ **Clinical Presentation of Intracerebral Hemorrhage**

Location	Occurrence (%)	Clinical Signs	Nonhypertensive (%)	Mortality (%)
Putamen	28–42	Motor and sensory deficit; depressed consciousness	10	20
Thalamus	10–26	Sensory and motor deficit; depressed consciousness; homonymous hemianopia	10	40
Subcortical white matter (lobar)	19–30	Higher incidence of seizures; coma unlikely; other symptoms depend on involved lobe	65	20
Cerebellum	8–15	Ataxia, cranial neuropathies; ± depressed consciousness	15	Coma 75 Other 17
Brainstem	4–11	Coma, decerebrate posturing, pinpoint reactive pupils, cranial neuropathies	30	85

Adapted from Thrift AG, Donnan GA, McNeil JJ: Epidemiology of intracerebral hemorrhage. Epidemiol Rev 17:361, 1995.

sensitive for detecting an underlying structural etiology, but the rapidity, availability, and ease of interpretation of CT favor its initial use. Contrast-enhanced head CT scan may show evidence of persistent hemorrhage at the time of presentation, the so-called "dot" or "spot" sign, which is associated with hematoma expansion and poorer prognosis. Vascular imaging is required whenever aneurysmal subarachnoid hemorrhage is possible, such as in cases with a large amount of subarachnoid blood, and should be considered for all patients without a clear etiology. Early MRI may be indicated if a structural etiology is suspected, but findings are often obscured by the hemorrhage in the acute phase. A scan delayed by 4 to 8 weeks may provide more useful information if urgent diagnosis is unnecessary. MRI is also useful in diagnosing cavernous malformations and may suggest cerebral amyloid angiopathy.

Treatment is generally supportive, although surgical intervention is indicated in rare cases. Severe hypertension is common after intracerebral hemorrhage, in part because it is a response to elevated intracranial pressure and brain injury. In patients with a systolic blood pressure of 150 to 220 mmHg, acute lowering of systolic blood pressure to 140 mmHg is probably safe. Current consensus guidelines suggest treating with antihypertensive medications for systolic blood pressure greater than 180 mmHg or mean arterial pressure greater than 130 mmHg, although studies to determine optimal blood pressure control after intracerebral hemorrhage suggest that targeting a systolic blood pressure of <160 or <140 mmHg is reasonable. Increased intracranial pressure may lead to coma and is treated with ventricular drainage, osmotherapy, or hyperventilation.

Surgical evacuation of primary intracerebral hemorrhages is commonly performed when there is posterior fossa hemorrhage with a risk of brainstem compression or when there is evolving neurologic deterioration in patients with lobar hemorrhages and other prognostic signs are favorable. For supratentorial intracerebral hemorrhages, studies have failed to establish a benefit of early surgical evacuation of the hematoma over a strategy of initial conservative treatment followed by surgical evacuation only if necessitated by neurologic deterioration, even among the subgroup of patients with lobar hemorrhage that are near the cortical surface. In practice though, patient selection and decisions on offering surgical interventions for supratentorial intracerebral hemorrhages are often individualized and variable. In recent years, there has been increasing interest in evaluating minimally invasive techniques for hematoma evacuation, although whether a definitive clinical benefit of these approaches will ultimately be demonstrated is unknown.

After the acute period, aggressive treatment of hypertension is indicated. In addition to reducing cardiovascular disease and ischemic stroke, treating hypertension substantially reduces the risk of intracerebral hemorrhage.

LACUNAR INFARCT

The term *lacune* was first introduced in 1843 by M. Durand-Fardel to describe small, subcortical areas lacking gray and white matter. These lesions were attributed to infarct and associated with particular clinical presentations by Marie and Ferrand more than 50 years later. In the 1950s, Miller Fisher reintroduced the term into modern neurology through his descriptions of the clinical and pathologic presentation which recognized the importance of hypertension as an etiology and a theory of pathogenesis that survives today.

Less than 2 cm in diameter, lacunes are small infarcts that result from occlusion of small penetrating branches arising from large arteries (Fig. 7-7). There is general agreement about the definition of lacune, but much argument about the interrelationship between lacunar infarcts, lacunar strokes (symptomatic lacunes), lacunar syndromes (symptom complexes often associated with lacunar strokes), and lacunar disease (lacunes due to intrinsic small-vessel changes). Arguments arise from imperfect correlations between these entities. First, not all lacunes produce lacunar strokes because some are silent. Second, lacunar syndromes are sometimes associated with large-vessel strokes. Third, lacunes are produced by intrinsic small-vessel disease and by other etiologies.

The majority of lacunes are located in the basal ganglia and thalamus, with the remainder in the internal capsule, pons, cerebellum, and subcortical white matter. Approximately 20 to 30 percent of ischemic strokes are due to lacunes. Lacunes are often found incidentally on MR scanning, particularly in older patients, and the vast majority of those with a lacune identified on imaging deny a history of stroke or transient ischemic attack (TIA). These “silent” lacunes are associated with impairment in cognitive and functional tasks, suggesting that the overall clinical burden of lacunes may be greater than previously suspected.

Hypertension is one of the most important risk factors for development of lacunes. However, the strength of the association may be no greater for lacunes than for other forms of ischemic stroke, and hypertension is not always present in lacunar disease. Elevation in the level of serum creatinine is independently associated with lacunar infarction, perhaps because it is a marker for chronic end-organ damage from hypertension in the small vessels of both the kidneys and the brain.

Diabetes mellitus is a risk factor for symptomatic lacunes, approximately doubling the risk. However, the influence of diabetes on lacunar stroke does not appear to differ from its effect on other ischemic stroke subtypes. This is also true for cigarette smoking, which doubles the risk of all ischemic strokes, including lacunes. Carotid artery stenosis is associated with an increased risk of lacunar stroke, with studies suggesting that the risk of a symptomatic lacune is doubled with carotid stenosis of 50 percent

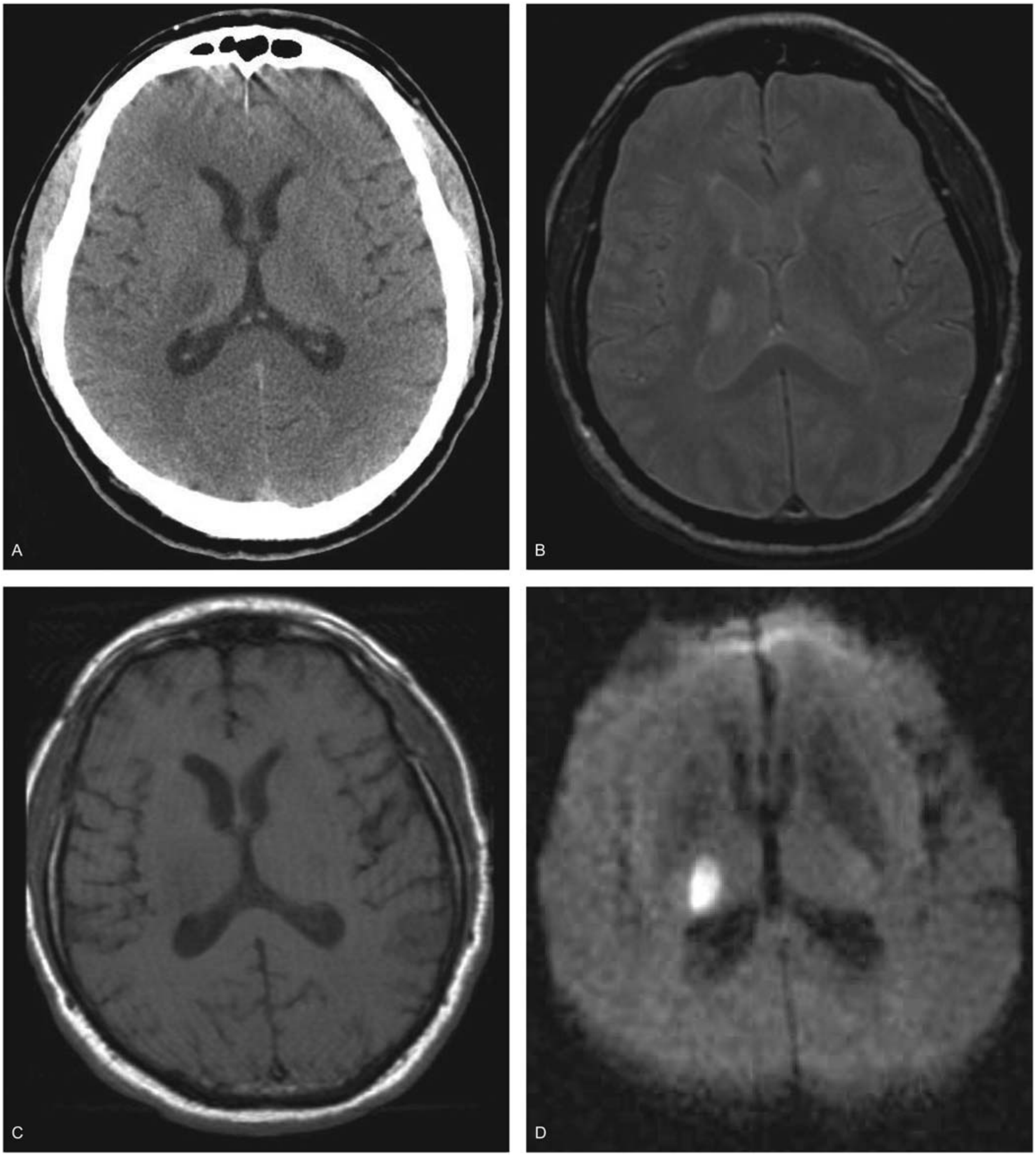

FIGURE 7-7 ■ An acute right thalamocapsular lacunar stroke producing a left sensorimotor syndrome. The lesion was hypodense on noncontrast head CT, *A*. With brain MRI, it was hyperintense on T2-weighted images, *B*, inconspicuous on T1-weighted images, *C*, and hyperintense on diffusion-weighted images, *D*.

or greater. Cardiac disease is less common in patients with lacunes than in those with other ischemic stroke types.

The etiology of lacunes has been argued over bitterly. Some have suggested that the vast majority of lacunes are due to changes within small penetrating vessels, primarily because of chronic hypertension, but others have argued that emboli to small vessels and intracranial atherosclerosis are responsible for a significant number of lesions. Fisher produced much of the data supporting an intrinsic small-vessel disease mechanism. He found degenerative changes in small vessels that he termed lipohyalinosis and fibrinoid degeneration, characterized by layers of connective tissue within the vascular media, obstructing the lumen. These changes were proximal to infarcts in some cases. Atherosclerosis at the origin appeared responsible for other infarcts. Fisher recognized that emboli may be responsible for some lacunes. Animal models have shown that particles may embolize to small penetrating arteries, producing lacunes. The etiology of lacunes is likely multifactorial. Intrinsic small-vessel disease may predominate, but emboli and intracranial atherosclerosis almost certainly account for a significant minority of cases.

Several classic presentations of lacunar strokes have been described, termed the *lacunar syndromes*. Pure motor hemiparesis is the most common, accounting for nearly half of cases. Motor functions involving face, arm, and leg are impaired, but other neurologic functions are spared. The appearance is different from that with cortical strokes, in which deficits in sensation or cognition often accompany motor changes. Pure motor hemiparesis is not always due to a lacune, with 10 to 20 percent of cases attributed to a cortical stroke. When a lacune is responsible, it is most often located in the posterior limb of the internal capsule or in the basis pontis, but any other site along the path of corticospinal fibers can produce the syndrome.

Sensorimotor syndrome is the second most common lacunar syndrome, accounting for about 20 percent of cases. Weakness and numbness are present in varying degrees, usually involving the face, arm, and leg. The syndrome is most commonly produced by a lacune involving the lateral thalamus and internal capsule, but some cases are not due to lacunes.

Ataxic hemiparesis accounts for about 15 percent of lacunar syndromes. In the affected limbs, pyramidal weakness is combined with elements normally attributed to cerebellar ataxia. Intention tremor, exaggerated rebound, and irregular rapid alternating movements are superimposed on ipsilateral weakness. The findings are highly suggestive of a lacunar stroke, with almost all of these cases attributable to lacunes. Infarct locations are identical to those that cause pure motor hemiparesis.

Among patients with lacunar syndromes, about 10 percent have a pure sensory stroke, characterized by impaired sensation without other accompanying neurologic deficits. When the face, arm, and leg are involved, the lesion is nearly always a lacune in the contralateral thalamus. A lesion in the medial lemniscus in the midbrain or rostral pons may occasionally produce an identical syndrome. Pain and dysesthesia in the affected region may accompany the lesion acutely or may be delayed by weeks to months.

Many other lacunar syndromes have been described, including clumsy-hand dysarthria, hemiballism, and pure motor hemiparesis combined with various eye movement abnormalities. Although lacunes occur more commonly in certain regions of the brain, they can occur anywhere, producing a multiplicity of potential syndromes. Even signs generally attributed to cortical lesions may be produced by lacunes, including aphasia, abulia, confusion, and neglect.

Prognosis for recovery after a lacunar stroke is generally more favorable than for ischemic strokes due to the occlusion of major vessels, although symptoms may occasionally worsen in the first few days after symptom onset. Recurrent stroke and mortality rates are also lower than for other stroke subtypes.

Diagnostic imaging has been recommended for all those presenting with lacunar syndromes. An immediate head CT scan will rule out hemorrhage as an etiology but may not distinguish lacunes from large-vessel infarctions. MRI provides more definitive confirmation, and MR or CT angiography may suggest intracranial atherosclerosis. For lacunar strokes in the internal carotid distribution, carotid artery imaging should be performed because a stenosis proximal to the lacune would generally be considered symptomatic.

Tissue plasminogen activator is effective in patients judged to have small-vessel occlusive strokes. In fact, absolute improvements in favorable outcomes may even be greater for small-vessel strokes than for large-vessel occlusive and cardioembolic strokes. Furthermore, the correlation between lacunar stroke and lacunar syndrome is so poor that a diagnosis of nonthrombotic small-vessel occlusion cannot be made with accuracy. Therefore, tissue plasminogen activator should still be administered for lacunar syndromes.

Aspirin reduces the risk of subsequent ischemic stroke, regardless of etiology. Clopidogrel and the combination of dipyridamole/aspirin are alternatives for secondary prevention in those who cannot tolerate aspirin, although the incremental improvement in efficacy compared to aspirin is small.[6] Long-term combination therapy with aspirin and clopidogrel is generally not recommended to prevent recurrent stroke owing to increased bleeding risks.[7,8] However, short-term combination therapy (21 days) with aspirin and clopidogrel can be helpful in the acute period compared to aspirin alone in patients with high-risk TIA or minor stroke.[9,10]

Long-term anticoagulation with warfarin is generally indicated in patients with ischemic stroke when atrial fibrillation is identified. Control of hypertension reduces subsequent ischemic stroke risk, and risk reduction may be even greater for lacunes. Treatment of isolated systolic hypertension in elderly patients may be particularly helpful to prevent lacunar stroke.

PERIVENTRICULAR WHITE MATTER DISEASE

With improvements in head imaging, changes in the white matter surrounding the lateral ventricles are frequently recognized in the elderly, a finding termed *leukoaraiosis*. Head CT shows a periventricular mantle of hypodensity, often most profound at the frontal and occipital horns, which is hyperintense on T2-weighted MRI (Fig. 7-8). Age is the most important risk factor, with nearly all of those older than 65 years showing at least some evidence of such change. Clinically, the changes are most frequently associated with insidious declines in cognitive and motor performance, particularly on tests that depend on reaction time and speed.

These white matter lesions have been related to several distinct pathologic processes, including hypoperfusion injury, cerebral amyloid angiopathy, dilated perivascular spaces, axonal loss, astrocytic gliosis, and loss of ependymal integrity with resulting cerebrospinal fluid extravasation. Lesions contiguous with the ventricles show fewer histologic and molecular markers of ischemia than lesions in the deep subcortical areas, where they resemble areas of "incomplete" infarction on pathologic examination. Loss of vasomotor reactivity and autoregulation due to small-vessel vasculopathy is hypothesized to be a frequent cause of the ischemic changes. Leukoaraiosis may be an important clinical indicator of end-organ injury from hypertension, integrating information about cumulative exposure to

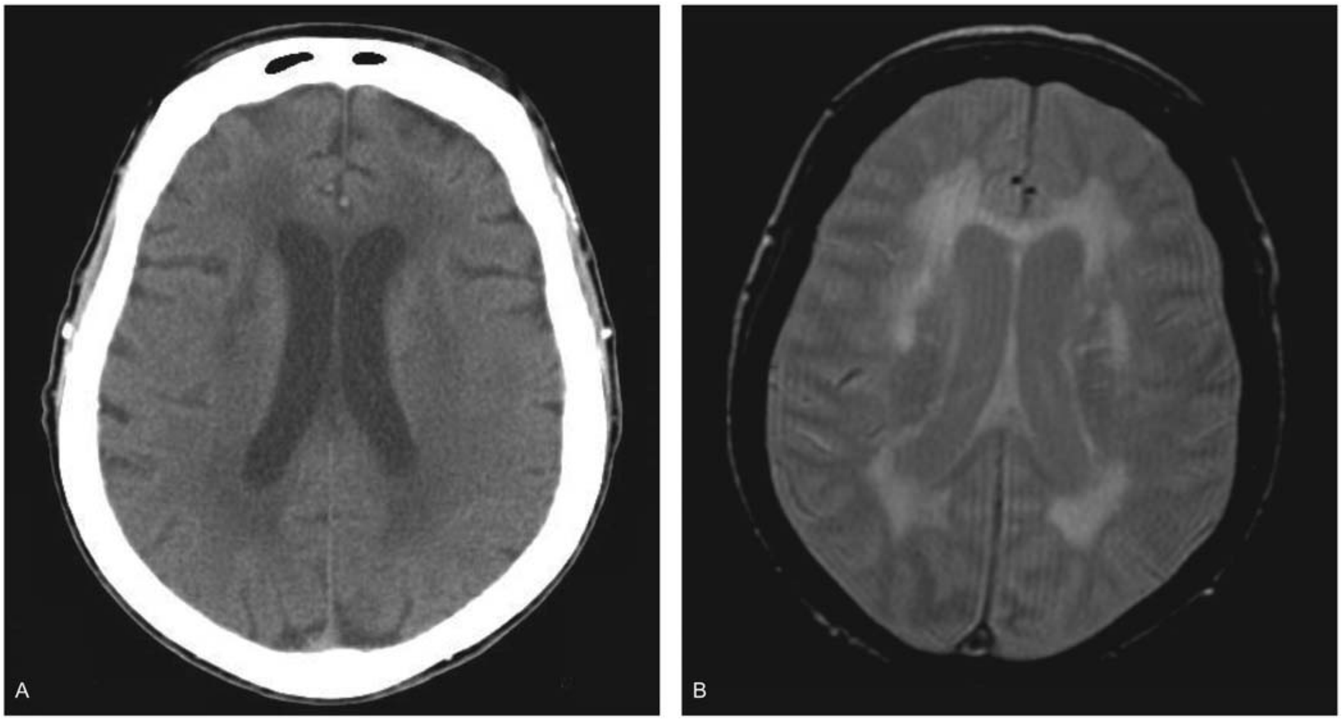

FIGURE 7-8 ▪ Imaging findings of periventricular white matter disease, with hypodensity on head CT, *A* and T2-weighted hyperintensities on brain MRI, *B*.

high blood pressure as well as susceptibility to injury. Individuals with white matter lesions in the brain are at high risk of incident stroke and other clinical cardiovascular events. White matter burden is also one of the strongest predictors of incident brain infarction defined by serial brain MRI.

CEREBRAL AUTOSOMAL-DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a dementing illness caused by mutations in the *NOTCH3* gene, which encodes a transmembrane receptor protein of unclear function and is characterized by a stepwise decline in cognitive and motor functions. Onset is early, beginning at 30 to 50 years of age, and it is often preceded by migraines with aura. Hypertension and diabetes are not associated. Head imaging shows multiple lacunes superimposed on periventricular white matter disease. Degeneration of vascular smooth muscle cells and granular deposits characterize vessels in the brain and in other regions. Involvement of the dermis allows confirmation by skin biopsy, although molecular genetic tests are available. No specific treatment is available.

CAROTID ARTERY STENOSIS

The first comprehensive description of carotid occlusion and stroke is attributed to Hunt, who in 1914 described a patient with decreased carotid pulsation contralateral to a hemiparesis. Autopsy confirmed a hemispheric infarct and showed patent intracranial vessels. With the advent of angiography and surgical exploration, internal carotid artery occlusion with recent thrombus was confirmed in the 1940s.

The precise contribution of internal carotid artery stenosis to the incidence of stroke is unclear because it is difficult to definitively attribute a stroke to the stenosis. Approximately 10 percent of ischemic strokes are due to internal carotid stenosis or occlusion and a substantial minority of the middle-aged population has some evidence of carotid plaque on ultrasonography. An asymptomatic carotid stenosis of more than 60 percent may be found in approximately 5 percent of 65-year-olds and this figure increases with age.

Hypertension is an important risk factor for carotid stenosis. Systolic hypertension is a powerful predictor of subsequent carotid stenosis, with the odds of carotid stenosis doubling with each 20-mmHg increase in systolic blood pressure. Systolic blood pressure is also a predictor of progression in patients with asymptomatic stenoses. Cigarette smoking, high serum cholesterol level, and increased homocysteine are other risk factors for carotid stenosis.

Internal carotid artery stenosis is produced by atherosclerosis just distal to the common carotid bifurcation. The pathophysiology of carotid artery stenosis is complex. Hypertension induces vascular remodeling, resulting in medial thickening, luminal narrowing, and impaired smooth muscle relaxation. These changes are concentrated in areas of nonlaminar flow, such as the common carotid bifurcation. Atherosclerotic plaques are thought to develop in these areas as a response to injury produced by hypertension, blood-flow abnormalities, lipids, and possibly infection. This initiating injury induces endothelial cell expression of cell adhesion molecules that mediate local extravasation of mononuclear cells, resulting in inflammation of vessel walls, with foamy, lipid-laden macrophages and T lymphocytes. Chronic injury leads to intimal hyperplasia and formation of complex plaques that may include a lipid core. When a plaque ruptures into the vessel lumen, thrombosis is induced, which may produce local occlusion, distal embolus, or, after organization, progressive luminal stenosis. Shear forces associated with a severe stenosis may induce platelet activation and thrombus formation without plaque rupture.

Clinically, symptomatic patients present with large-vessel ischemic strokes or TIAs in the distribution of the ophthalmic, middle, or anterior cerebral artery. Transient monocular blindness (amaurosis fugax), weakness, numbness, aphasia, or neglect may occur, depending on the affected region of the anterior circulation. Borderzone ischemia due to distal hypoperfusion in the anterior and middle cerebral artery territories presents with proximal upper and lower extremity weakness and numbness (i.e., "man-in-the-barrel" syndrome) and may indicate a critical stenosis or occlusion with inadequate collateral blood flow. Artery-to-artery emboli classically appear as cortical wedge-shaped infarcts, indistinguishable from emboli from other sources. Lacunar infarcts, often attributed to intrinsic small-vessel disease, probably represent embolic events from carotid artery stenoses in some instances because endarterectomy appears to reduce the risk of ipsilateral lacune.

A cervical bruit may be a sign of carotid stenosis, but it is absent in up to half of cases later confirmed to have stenosis exceeding 70 percent and is present in up to half of those without a severe stenosis. Therefore, carotid imaging studies are generally indicated for patients with anterior circulation ischemic strokes or transient ischemic attacks independent of a finding of a carotid bruit.

CT angiography, carotid Doppler ultrasonography, neck MR angiography, or catheter angiography is required for the determination of whether an internal carotid stenosis is present. CT angiography is often part of an initial emergency department for large-vessel occlusion stroke. Although CT angiography can reliably exclude the presence of significant carotid artery stenosis, it can sometimes overestimate the degree of stenosis, particularly when calcifications are present. In this setting, carotid Doppler ultrasonography can be a helpful second noninvasive study to confirm the degree of stenosis. MR angiography provides three-dimensional views and can be extended to include the intracranial vasculature. Catheter angiography is considered the gold standard but carries a small procedural risk. Therefore, it is generally preferable to obtain noninvasive imaging first and in most cases these noninvasive studies obviate the need for catheter angiography.

Aspirin has been shown to reduce risk of stroke and myocardial infarction in patients with ischemic stroke or TIA and carotid disease, with a risk reduction of about 10 to 20 percent. Some clinicians use anticoagulation with heparin to treat symptomatic carotid stenosis in the acute setting until a more definitive surgical or endovascular intervention can be applied, but there are no reliable data supporting this approach. Based on results in coronary artery disease, a process with similar pathophysiology, and on overall risk reduction of ischemic stroke, treatment with cholesterol-lowering agents may be of benefit even in those without hypercholesterolemia.

Urgent surgical removal of the obstructing plaque by endarterectomy is the established standard of therapy for symptomatic patients with carotid artery stenosis of at least 70 percent (Table 7-4). Endarterectomy also reduces recurrent stroke rates in patients (especially men) with symptomatic carotid stenoses of 50 to 69 percent, but the benefits of treatment are more modest and the consequences of procedural complications are even more important to consider since the baseline risk of recurrent stroke is lower than with stenosis greater than 70 percent. Endarterectomy is not beneficial in patients with stenosis less than 50 percent and is generally impractical in those with carotid artery occlusion, unless it is considered a part of an acute large-vessel occlusion stroke syndrome (e.g., with a concurrent ipsilateral MCA

TABLE 7-4 ■ Yearly Ipsilateral Stroke Rates with Carotid Artery Stenosis Based on 5-Year Follow-up

	Endarterectomy* (%)	Medical Therapy (%)	*P* Value	NNT 5-Year†
Symptomatic Stenosis				
NASCET ≥ 70%	2.6	5.2	<0.001	8
50–69%	3.1	4.4	0.045	15
30–49%	3.0	3.7	0.16	
ECST‡ ≥ 60%	1.8	4.0	<0.001	9
40–60%	2.8	1.6	NS	
Asymptomatic Stenosis				
ACAS ≥ 60%	1.0	2.2	0.004	17

ACAS, Asymptomatic Carotid Atherosclerosis Study; ECST, European Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial; NNT, number needed to treat; NS, not significant.

*Includes any perioperative stroke or death.

†NNT with surgery to prevent one ipsilateral stroke in 5 years.

‡Degree of stenosis converted to NASCET criteria (diameter at narrowest/diameter in most proximal normal internal carotid artery). End-point included perioperative death or major strokes and was calculated based on mean 6-year follow-up.

occlusion). The risk of stroke with medical therapy is greater in those with cerebral events than ocular events, with plaque surface irregularity consistent with ulceration, with a recent symptomatic event, and with greater degrees of stenosis. The risk of surgery is greater in females, in those with severe hypertension, and in those with peripheral vascular disease. These prognostic factors may be useful in fine-tuning patient selection for endarterectomy.

For patients with asymptomatic carotid artery stenosis, endarterectomy also prevents stroke when there is stenosis of at least 60 percent as assessed by carotid ultrasonography, but the benefits are more diffuse, and therefore current guidelines recommend consideration of endarterectomy for asymptomatic stenosis for patients with a surgical risk less than 3 percent and life expectancy of at least 5 years. Many of the pivotal studies for carotid stenosis were conducted decades ago, before the widespread use of statins for example, and the recurrent stroke risk with medical management seems to be improving over time. Therefore, it is unclear whether carotid revascularization interventions (carotid endarterectomy or carotid artery stenting) would still be favored when compared to modern medical regimens—a question that is being evaluated in the ongoing CREST-2 trial.[11]

Endovascular angioplasty and stenting is an alternative approach to treatment of carotid stenosis, and stenting has been shown to be not inferior to endarterectomy in patients with both symptomatic and asymptomatic stenoses who have comorbidities associated with high surgical risk during endarterectomy. A large-scale trial comparing endarterectomy and stenting in more representative patient populations showed similar long-term outcomes with both approaches; there was an increased risk of periprocedural stroke with endovascular stenting and a higher risk of myocardial infarction with endarterectomy, although these complications are not directly comparable given the relative ease of detecting a troponin elevation with a simple blood test as opposed to detecting a stroke that would likely have to be symptomatic to justify a confirmatory neuroimaging test.[12]

INTRACRANIAL ATHEROSCLEROSIS

Atherosclerosis involving the large intracranial vessels causes about 10 percent of ischemic strokes. African Americans, Hispanics, and Asians have a higher prevalence of intracranial atherosclerosis, and a relatively lower prevalence of extracranial carotid artery stenosis compared with Caucasians. Extracranial carotid atherosclerosis is associated with a higher prevalence of peripheral vascular and coronary artery disease, but intracranial atherosclerosis is not. Given racial and risk factor distribution differences, it seems appropriate to consider intracranial atherosclerosis an entity distinct from carotid artery disease rather than as an additional manifestation of widespread atherosclerotic changes.

Hypertension is an important risk factor for intracranial atherosclerosis, with a two- to threefold higher risk of disease in those with a history of hypertension. Smoking may be the most important risk factor, with a risk that steadily increases with the number of pack-years of smoking exposure. Diabetics have about three times the risk of developing intracranial atherosclerosis. Hypercholesterolemia also increases risk, but probably to a lesser degree. The relative contribution of these factors to intracranial atherosclerosis as opposed to other stroke subtypes is unclear. The distribution of known risk factors probably accounts for some of the racial differences.

There are intriguing differences in the pathophysiology of intracranial atherosclerosis and other forms of vascular disease. Intracranial arteries are less susceptible to hypercholesterolemia than are extracranial arteries, and atherosclerotic plaque rupture appears to be less common. Release of endothelial adhesion molecules is greater with intracranial atherosclerosis than in other ischemic stroke subtypes, suggesting that inflammation is particularly important in its pathogenesis.

Clinical presentation is characterized by large-vessel or penetrating artery ischemia. The middle cerebral artery is most commonly involved, followed in order by the basilar, intracranial internal carotid, anterior cerebral, and posterior cerebral arteries. Thrombosis at the site of the stenosis may lead to hypoperfusion in the entire distal territory or to artery-to-artery embolus indistinguishable from events caused by extracranial carotid artery stenosis or cardiac embolus. Basilar thrombosis may result from underlying atherosclerosis in the basilar or vertebral arteries or after cardiac embolus; it is a life-threatening, often delayed diagnosis characterized by coma, quadriplegia, and cranial nerve findings. Involvement of the origin of penetrating small vessels may produce lacunar infarctions. Presentation with TIA prior to infarction is more common with intracranial atherosclerosis than with other stroke subtypes.

Intracranial MR or CT angiography may reveal narrowing or occlusion of large vessels. Time-of-flight MR angiography is prone to artifacts and may suggest a stenosis where none is present; sensitivity is low for medium-sized and smaller vessels, although contrast-enhanced MR angiography can mitigate these issues. CT angiography offers a true luminal image but involves use of ionizing radiation. Transcranial Doppler ultrasonography shows increased blood flow velocities in large stenotic vessels. Its sensitivity and specificity are also low, so it may be most useful as an adjunct. Catheter angiography is the gold standard for establishing the diagnosis, but it is associated with a procedural stroke risk under 1 percent. Given the risk of angiography, it is justified only if results will alter treatment decisions.

Prognosis in symptomatic patients is poor but can be improved with aggressive medical therapy. Stenoses generally become more severe with time, but regression in some segments may occur. Studies have shown that the combined outcome of stroke, brain hemorrhage, or vascular death is similar with warfarin compared with high-dose aspirin, although bleeding risks are greater with warfarin. More recent studies comparing intracranial angioplasty stenting compared to an aggressive medical regimen including dual-antiplatelet therapy with aspirin and clopidogrel along with a statin, demonstrated a lower risk of stroke or death with aggressive medical management, which some speculate is due to improvements in medical therapy in recent years; as a result, stenting is not commonly recommended.[13]

Patients with intracranial atherosclerosis also have a theoretical risk of hypoperfusion distal to the stenosis when blood pressure is lowered. Since these lesions are less commonly corrected compared with those in the carotid artery, some physicians may be less aggressive about treating hypertension in these patients. There is currently no evidence to justify higher long-term blood pressure thresholds in patients with intracranial atherosclerosis or to support the belief that lower blood pressures could increase the risk of infarction distal to a stenosis. In fact, targeted blood pressure management was an important component of aggressive medical treatment in studies comparing it with angioplasty and stenting.

AORTIC ARCH ATHEROSCLEROSIS

The aortic arch can be a source of emboli to the brain. Ulcerated plaque in the aortic arch is more common in patients with ischemic stroke compared with control populations, and thickened aortic arches are identified more often on transesophageal echocardiograms in stroke patients than in control subjects. In those with no other identified etiology for stroke, a thickened aortic arch is present about 25 percent of the time. Aortic arch atherosclerosis is more strongly associated with peripheral vascular disease than with carotid stenosis. Epidemiologic studies have been small, and only cigarette smoking has been identified as an important risk factor. Hypertension, diabetes, and hypercholesterolemia may be risk factors, but this has not been confirmed.

Strokes and TIAs produced by aortic atherosclerosis are identical to those produced by cardiac sources of emboli. Large-vessel territories are generally affected, producing weakness and numbness in similar distributions often along with cortical signs, such as aphasia and neglect.

Atherosclerotic plaque in the aortic arch that is 4 mm thick or larger carries a particularly high risk of recurrent stroke, even after accounting for other risk factors. The relative efficacy of antiplatelet therapy compared to anticoagulation to prevent recurrent stroke in patients with aortic arch disease remains unclear.[14] Aortic endarterectomy has been performed in some patients who have failed medical therapy, but it has not been studied systematically.

CARDIAC EMBOLUS

Hypertension increases the risk of myocardial infarction and atrial fibrillation. These diseases are associated with increased stroke risk from cardiac embolus, as discussed in Chapter 5.

DEMENTIA

There is evidence from multiple cohort studies that cardiovascular risk factors, including hypertension, are risk factors for the development of dementia and cognitive impairment. The biologic basis for these associations remains unresolved. Although there are some data to support a direct association between hypertension and Alzheimer pathology, there is increasing recognition that most individuals with dementia have a combination of neurodegenerative and vascular pathology. The association between hypertension and dementia is likely to be mediated in part by the accumulation of subclinical vascular injury in the brain, including infarcts and leukoariosis, that results in the interruption of cognitive networks. Whether this process is simply additive to the cognitive effects of Alzheimer pathology or whether there is synergism between the two processes remains unresolved.

Whether treatment of hypertension will make a large impact on the occurrence of dementia outside of its established benefits for stroke prevention is unclear. Some studies have suggested that a calcium-channel blocker for primary prevention can substantially reduce the risk of dementia but other studies have not confirmed this finding. Some studies have suggested that active therapy with an ACE-inhibitor and diuretic can reduce the risk of dementia when used for secondary prevention, but these potential benefits are more difficult to establish for primary prevention.

Although it hardly seems necessary to define additional benefits of treating hypertension, the recognition that cognitive decline may be an important manifestation of end-organ injury from hypertension has important implications for testing new treatments for cerebrovascular disease, assessing risk of stroke, and encouraging adherence to treatment. If hypertension therapy is proven to prevent dementia among those without stroke, the cost–benefit ratio for more aggressive screening and therapy could also be substantially improved, an important issue given that the elderly, who are at highest risk of dementia, are also the least likely to have their hypertension adequately treated. Some have suggested that aggressive blood pressure reduction could worsen cognition, particularly among those with loss of cerebral autoregulation due to small-vessel arteriopathy. Therefore, the benefits of blood pressure therapy for cognition will need better definition in order to optimize treatment regimens.

HYPERTENSIVE ENCEPHALOPATHY

Hypertensive encephalopathy is one of several forms of posterior reversible encephalopathy syndrome (PRES), a syndrome also encompassing other etiologies, including renal failure, immunosuppressive therapy, and eclampsia.

The incidence of hypertensive encephalopathy is thought to have declined with greater use of antihypertensive medications. It tends to occur with a sudden elevation in blood pressure rather than with chronic hypertension. A number of medical conditions are known precipitants. Hyperadrenergic states may be responsible, including pheochromocytoma, tyramine ingestion with monoamine oxidase inhibitors, abrupt antihypertensive discontinuation, lower gastrointestinal irritation in paraplegic patients, and stimulant medications. Structural precipitants include aortic coarctation and renal artery stenosis. Acute or chronic renal failure is another cause, probably through volume overload in addition to hypertension, and human recombinant erythropoietin may be a precipitant. In patients in the postoperative period after endarterectomy, changes ipsilateral to the surgery may be identical to those seen with hypertensive encephalopathy, even in the absence of blood pressure elevation, probably because vessels compensate for chronic hypoperfusion distal to a severe stenosis and sudden return of blood flow produces relative hypertension.

Hypertensive encephalopathy is associated with vasogenic cerebral edema, particularly severe in the posterior regions of the cerebral hemispheres, which is sometimes sufficient to result in herniation. The pathophysiology linking hypertension and cerebral edema has been argued. At mean arterial pressures greater than 120 to 170 mmHg, cerebral blood flow increases linearly with blood pressure, and some have argued that this is the threshold for hypertensive encephalopathy, when a "breakthrough of autoregulation" occurs. Angiotensin II may contribute to the formation of edema by increasing cerebrovascular permeability through oxygen free radicals. A predilection toward involvement of the posterior hemispheres may be due to differential vascular innervation by the sympathetic nervous system.

Hypertensive encephalopathy is a neurologic emergency that can lead to death if untreated. Diagnosis may be delayed when the connection between acute neurologic dysfunction and hypertension is not obvious. High blood pressure may be attributed to an underlying neurologic condition or agitation rather than identified as the causative agent. Headache is a common early complaint,

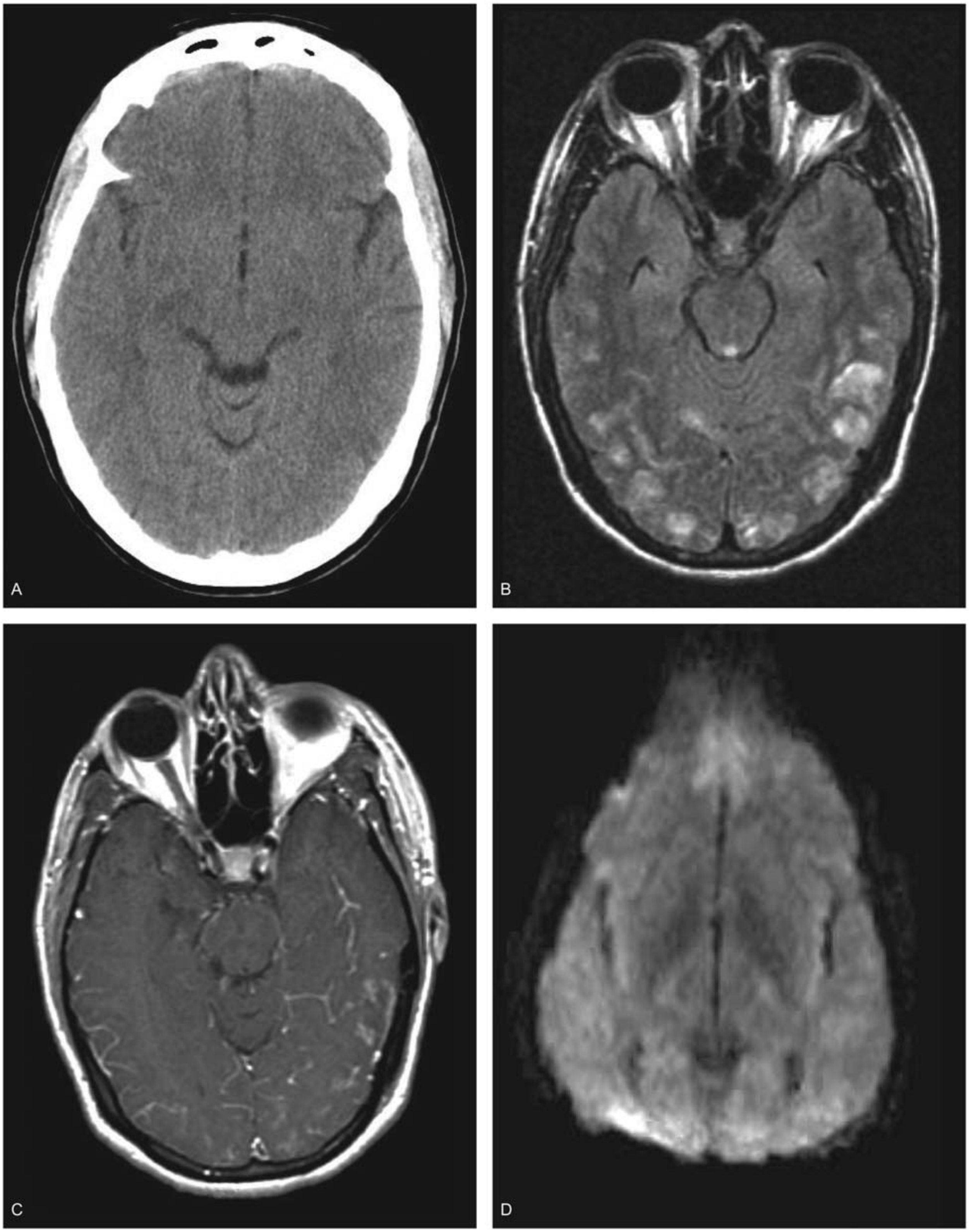

FIGURE 7-9 ■ A patient with eclampsia. Typical findings in hypertensive encephalopathy are identical and include normal or subtle hypodensity on head CT, *A*, subcortical hyperintensities on brain MRI fluid-attenuated inversion recovery (FLAIR) sequences, *B*, enhancement with gadolinium on T1-weighted images, *C*, and no abnormality on diffusion-weighted MRI, *D*.

sometimes accompanied by nausea and vomiting. Confusion with either agitation or lethargy may proceed to obtundation and coma if the process is untreated. Visual disturbance is frequent due to involvement of the retina and occipital lobes, with papilledema and subjective blurred vision, hemianopia, or cortical blindness. Other cortical deficits may occur, including neglect, aphasia, and weakness. Focal or generalized seizures may complicate the course.

Head imaging should be performed to exclude hemorrhage or a structural etiology for both the encephalopathy and the hypertension. Since increased intracranial pressure can result in severe hypertension, which may be required to maintain cerebral perfusion, an urgent study is necessary. Head CT may show hypodensity in subcortical white matter, often most obvious in the occipital lobes (Fig. 7-9). MRI findings may be dramatic, with multifocal T2-weighted hyperintensities particularly apparent in fluid-attenuated inversion recovery sequences. These changes are distinguished from infarcts by sparing of the cortex and absence of reduced diffusion, as expected with vasogenic edema. When cerebral edema is severe, lumbar puncture should be avoided.

Once a structural etiology has been excluded, treatment of hypertension must be initiated. Target blood pressures are tailored to individual patients, with the goal of returning patients to their recent baseline. For patients without a history of hypertension, normal blood pressure parameters are appropriate, but for those with chronic hypertension, an abrupt return to 140/90 mmHg may result in hypoperfusion owing to chronic vascular compensatory changes. Close observation and intravenous antihypertensives are generally indicated. Intravenous dihydropyridine calcium-channel blocking agents and ACE-inhibitors are effective and easy to titrate and may have less profound effects on cerebral vessels. The underlying cause of the hypertensive episode should be sought. Prognosis in treated patients is generally good. Neurologic deficits usually recover completely within 2 weeks.

ECLAMPSIA

Eclampsia can be considered a form of posterior reversible encephalopathy. Occurring during the second half of pregnancy or the puerperium, eclampsia presents with proteinuria and clinical and imaging manifestations identical to hypertensive encephalopathy. Hypertension may not be severe, so additional effects on brain endothelial cell permeability with evidence of generalized endothelial cell dysfunction with abnormal vascular reactivity are probably important. An underlying inflammatory response may be causative, but other potential etiologies have also been hypothesized.

Cerebral venous sinus thrombosis is another complication of pregnancy and delivery and can present with findings similar to those seen with eclampsia. MRI and venography are usually adequate to distinguish the two diseases, showing obstructed venous sinuses or ischemia with cytotoxic edema on diffusion-weighted sequences in cerebral venous sinus thrombosis.

Treatment includes delivery of the fetus and intravenous magnesium. Other antihypertensive medications and anticonvulsants can also be used. Prognosis is good if treatment is initiated quickly.

IMMUNOSUPPRESSION

Several immunosuppressive agents produce a posterior reversible encephalopathy identical to hypertensive encephalopathy. Cyclosporine is the classic example, and it may produce neurologic symptoms at therapeutic levels and without evident hypertension. Tacrolimus, interferon-α, cytarabine, and fludarabine are some of the other medications that have also been associated. An alteration in the permeability of cerebral endothelial cells has been postulated. Lowering blood pressure and discontinuing immunosuppression generally reverses the process.

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CHAPTER

8

Dysautonomia, Postural Hypotension, and Syncope

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NON-NEUROLOGIC CAUSES OF POSTURAL HYPOTENSION
- Cardiovascular Disorders
- Alterations of Effective Blood Volume
- Drugs
- Endocrine and Metabolic Disorders
- Inadequate Postural Adjustments
- Age

AUTONOMIC REGULATION OF THE HEART AND BLOOD VESSELS

NEUROLOGIC CAUSES OF POSTURAL HYPOTENSION
- Central Lesions
- Spinal Injury
- Root and Peripheral Nerve Lesions
  - *Hereditary Disorders*
  - *Metabolic Disorders*
  - *Infectious, Inflammatory, and Immune-Mediated Disorders*
  - *Iatrogenic Disorders*
- Toxic Exposure
- Primary Degeneration of the Autonomic Nervous System
- Miscellaneous Disorders
  - *Postural Orthostatic Tachycardia Syndrome*

SYMPTOMS OF DYSAUTONOMIA
- General
- Syncope
  - *Postural Hypotension*
  - *Neurally Mediated Syncope*
  - *Cardiac Syncope*
  - *Hyperventilation*

EVALUATION OF AUTONOMIC FUNCTION
- Postural Change in Blood Pressure
  - *Tilt-Table Testing*
- Postural Change in Heart Rate
- Valsalva Maneuver
- Other Cardiovascular Responses
- Digital Blood Flow
- Cold Pressor Test
- Plasma Norepinephrine Level and Infusion
- Response to Tyramine
- Sweat Tests
- Other Studies
  - *Pupillary Responses*
  - *Radiologic Studies*

PATIENT MANAGEMENT
- Treatment
  - *Nonpharmacologic Measures*
  - *Pharmacologic Treatment*
- General Precautions in Dysautonomic Patients

When a healthy person stands up after being recumbent, approximately 500 ml of blood (or more) pools in the vessels of the legs and abdomen, causing a reduction in filling pressure of the right atrium and thus a decrease in cardiac output and systemic blood pressure. This leads to changes in baroreceptor activity and thus to changes in impulse traffic in the ninth and tenth cranial nerves. These changes affect the activity of the brainstem vasomotor center, which, in turn, influences the autonomic neurons in the intermediolateral cell columns of the thoracolumbar spinal cord, producing reflex peripheral vasoconstriction and an increase in force and rate of myocardial contraction (Figs. 8-1 and 8-2). Cardiopulmonary reflexes, subserved by vagal afferent fibers from mechanoreceptors in the heart and stretch receptors in the lungs, contribute to maintenance of the blood pressure, acting synergistically with the baroreceptor reflexes. The venoarteriolar axonal reflexes may also be important in limiting blood flow to the skin, muscle, and adipose tissues. Standing up also leads to release of norepinephrine. Venous return is aided during maintenance

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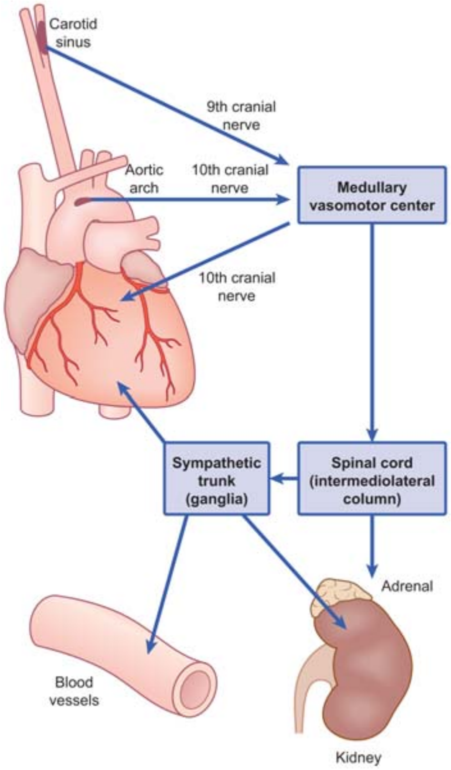
Carotid sinus
9th cranial nerve
Aortic arch
10th cranial nerve
Medullary vasomotor center
10th cranial nerve
Sympathetic trunk (ganglia)
Spinal cord (intermediolateral column)
Adrenal
Blood vessels
Kidney

FIGURE 8-1 ■ Anatomy of the autonomic pathways involved in maintaining the blood pressure on standing.

of the upright posture by mechanical factors, such as the tone in the leg muscles and the pumping action of these muscles during walking, and by maneuvers that increase intra-abdominal pressure. This has important therapeutic implications (see p. 141). In addition, there is secretion of antidiuretic hormone (arginine vasopressin) and activation of the renin-angiotensin-aldosterone system, so that salt and water are conserved and blood volume increases. These, however, are typically longer-term rather than immediate control mechanisms.

Postural hypotension is defined as a decrease of at least 20 mmHg in systolic pressure or 10 mmHg in diastolic pressure within 3 minutes of standing. It occurs when there is a failure of the autoregulatory mechanisms that maintain the blood pressure on standing. It may therefore occur with any neurologic disorder that impairs baroreceptor function, disturbs the afferent input from these receptors, directly involves the brainstem vasomotor center or its central connections, or interrupts the sympathetic outflow pathway either centrally or peripherally. It may also occur with a number of non-neurologic disorders, and it is important to consider these disorders if patients are to be managed correctly. Postural hypotension is associated with an increased risk of falls and consequent morbidity and mortality, especially among the elderly.

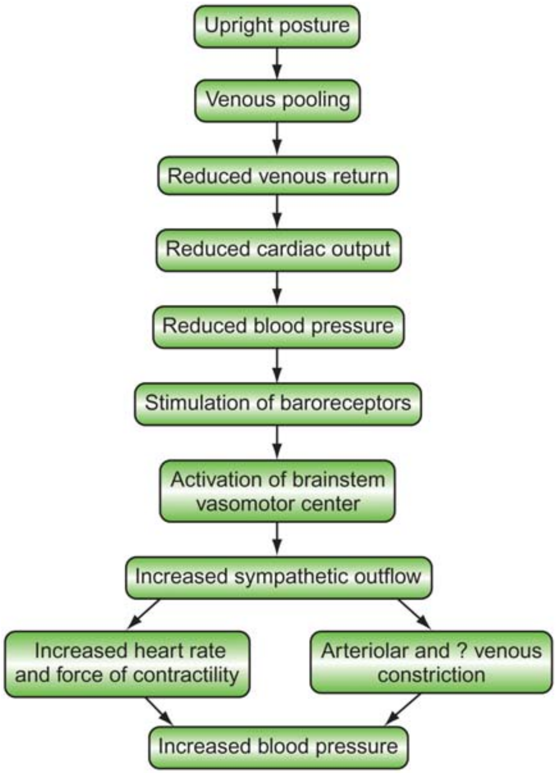
Upright posture
Venous pooling
Reduced venous return
Reduced cardiac output
Reduced blood pressure
Stimulation of baroreceptors
Activation of brainstem vasomotor center
Increased sympathetic outflow
Increased heart rate and force of contractility
Arteriolar and ? venous constriction
Increased blood pressure

FIGURE 8-2 ■ Sequence of events that ensure maintenance of the blood pressure after adoption of the upright posture. Only the immediate cardiovascular changes are shown. As indicated in the text, a variety of other humoral mechanisms is also activated.

NON-NEUROLOGIC CAUSES OF POSTURAL HYPOTENSION

Cardiovascular Disorders

A variety of cardiac disorders may lead to postural hypotension or even syncope. Pathologic processes such as mitral valve prolapse, aortic stenosis, or hypertrophic cardiomyopathy may limit cardiac output. Cardiac outflow may also be blocked in rare instances by a thrombus or myxoma when the patient is in the upright position. Certain paroxysmal cardiac dysrhythmias (bradycardias or tachycardias) may occur with activity or on standing and produce episodic hypotension or syncope; however, disturbances of cardiac rhythm are common in asymptomatic elderly persons, and their presence must be interpreted with caution.

In patients with congestive heart failure, the heart rate and level of sympathetic tone may be such that compensatory adjustments cannot be made when the patient stands, and postural hypotension therefore results.

Alterations of Effective Blood Volume

Postural hypotension can occur because of loss of effective blood volume. Normal adults can withstand the loss of 500 ml of blood or bodily fluids with few if any symptoms, but greater volume depletion may occur acutely for a variety of reasons (e.g., hemorrhage or burns) and cause a postural drop in blood pressure. Hyponatremia and Addison disease may also lead to an absolute reduction in blood volume. Postural hypotension may occur owing to venous pooling in patients with severe varicose veins or congenital absence of venous valves or because of poor peripheral resistance and reduced muscle tone in patients with paralyzed limbs. Similarly, it may occur during the late stages of pregnancy owing to obstructed venous return by the gravid uterus. Marked vasodilatation, such as occurs in the heat or with the use of certain drugs or alcohol, sometimes causes postural hypotension.

Drugs

Numerous drugs may produce postural hypotension, including those given to treat neurologic disorders (e.g., dopamine agonists, levodopa, and selective monoamine oxidase B inhibitors) and psychiatric disturbances (e.g., tranquilizing, sedative, hypnotic, and antidepressant agents). Antihypertensive drugs, diuretics, phosphodiesterase inhibitors, and vasodilators commonly lead to postural hypotension as a side effect, as do α-blockers (e.g., tamsulosin). Insulin may cause nonhypoglycemic postural hypotension in diabetic patients with autonomic neuropathy, possibly because of vasodilatation and reduced venous return in the absence of functioning compensatory mechanisms or because of impaired baroreceptor responses to changes in arterial pressure. Iatrogenic and toxic autonomic neuropathy is considered later.

Endocrine and Metabolic Disorders

Autonomic neuropathy, with consequent postural hypotension, is a major and common complication of diabetes. Postural hypotension may be a feature of Addison disease, hypopituitarism, myxedema, thyrotoxicosis, pheochromocytoma, carcinoid syndrome, and hypokalemia. It may also occur with anorexia nervosa. Anemia may exacerbate or cause postural hypotension.

Inadequate Postural Adjustments

Prolonged bed rest may result in postural hypotension when patients first begin standing again, but this problem is self-limited. Its cause is poorly understood, but it may be multifactorial. Carotid baroreceptor function is impaired, cardiac vagal activity is reduced, blood pooling is increased in the legs because of greater venous compliance, the total circulating blood volume and central venous pressure are reduced, and the red cell mass may decline. Prolonged bed rest also leads to an increased incidence of cardiac dysrhythmias. In otherwise healthy subjects, vigorous exercise to the point of exhaustion may also cause a postural decline in blood pressure, possibly because of marked peripheral vasodilatation and venous pooling.

Age

Many patients older than 70 years have a decline in systolic pressure of 20 mmHg or more on standing, although in most instances this is asymptomatic. Several causes of reduced orthostatic tolerance with advancing age have been identified. Baroreflex sensitivity declines with age and certain adrenoreceptors exhibit reduced sensitivity. Loss of preganglionic neurons also occurs with age and becomes symptomatic when approximately 50 percent of the cells are lost. Diuretics (which are commonly taken by the elderly) reduce blood volume and may lead to postural hypotension. Finally, structural, mechanical, and functional changes in the vascular system,[1] such as loss of vascular elasticity and the occurrence of varicose veins, may be contributory, as may a reduction in the skeletal muscle mass. Prolonged bed rest, intercurrent illness, and adverse reactions to medication (especially antihypertensive drugs) may also be important.

Syncope is a common problem in the elderly. Often no precise explanation for it can be found, but postural hypotension is probably responsible in many instances. Nevertheless, it is best not to ascribe patients' symptoms to postural hypotension unless they can be reproduced by a demonstrable fall in blood pressure on standing. Many of the homeostatic mechanisms that maintain intravascular volume and blood pressure may be impaired with advancing age, as discussed earlier, so that syncope is more likely to occur. Indeed, in many elderly patients a number of factors can be found to account for syncope, and it is then difficult to determine which of these factors is responsible in any individual instance.

AUTONOMIC REGULATION OF THE HEART AND BLOOD VESSELS

The central nervous system (CNS) is important in regulating cardiovascular function. Various lower brainstem centers receive inputs from both the periphery and other central structures such as the cerebral cortex, temporal lobe, amygdala, hypothalamus, cerebellum, periaqueductal gray matter, and pontine nuclei. The nucleus tractus solitarius is the site of termination of baroreceptor, chemoreceptor, and cardiopulmonary afferent fibers; it connects with the nucleus ambiguus and dorsal nucleus of the vagus and with neurons in the lateral reticular formation that project to the cord in the bulbospinal pathway, thereby influencing the cardiovascular system.

The vagus nerve has a major role in regulating the heart rate responses to various maneuvers. The sympathetic nervous system is important in influencing vasomotor tone and peripheral vascular resistance, but the sympathetic outflow to different regions and structures is regulated separately. The sympathetic nervous system causes a vasoconstriction in response to the release of norepinephrine. The occurrence of vasodilatation in the limbs probably depends on reduced sympathetic activity, and, to a lesser extent, on axon reflexes and antidromic conduction, but some of the vessels in limb muscles are probably also supplied by sympathetic vasodilator cholinergic fibers.

Microneurographic studies in humans have shown that bursts of impulses occur rhythmically in sympathetic efferent vasomotor fibers to the skin and muscles and are time-locked to the pulse. This rhythmic activity depends on supraspinal mechanisms and is not seen below the level of a complete spinal cord transection. Such sympathetic impulse traffic to vessels in the limb muscles is markedly affected by baroreceptor activity, but not by brief mental stress, whereas the traffic in human cutaneous nerves is markedly increased by mental stress. High-pressure arterial baroreceptors are located primarily in the carotid sinus and aortic arch, from which afferent fibers pass to the brainstem in the glossopharyngeal and vagus nerves, respectively.

Sympathetic efferent activity is inhibited by an increase in the pressure in the carotid sinus and aortic arch, whereas a reduced pressure causes increased sympathetic activity and a peripheral vasoconstriction. The heart rate is also influenced by the baroreceptors and cardiopulmonary stretch receptors, so that a bradycardia occurs when the pressure is increased and a tachycardia when the blood pressure declines.

Change from recumbency to an erect posture causes blood to pool in the legs and lower abdomen. There is a slight fall in systolic blood pressure; this leads to baroreceptor activation, a peripheral vasoconstriction, and an increase in heart rate and contractile force. Compensatory changes in the splanchnic vasculature, constriction of venous beds, and activation of the renin-angiotensin system also occur.

The carotid baroreceptor reflexes seem to be more important in responding to the immediate changes in blood pressure that occur on standing, whereas the aortic baroreceptors assume a greater role with maintenance of the upright posture. The cardiopulmonary stretch receptors act synergistically with the baroreceptor reflexes. The venoarteriolar axon reflex, which is activated by venous distention in the legs and an associated increase in transmural venous pressure, is also important in ensuring an increase in limb vascular resistance with change to an erect posture. During activity, the baroreceptors are reset by an uncertain, probably neural, mechanism to allow the blood pressure to increase with exercise. Unmyelinated chemoreceptor afferent fibers from skeletal muscles are also activated, thereby increasing blood pressure and correcting any deficiency in muscle perfusion pressure during moderate to heavy exercise. In addition, activation of mechanically sensitive muscle receptors (muscle mechanoreflex) occurs, and these exercise pressor reflexes (peripheral neural reflexes originating in skeletal muscle) contribute significantly to cardiovascular regulation during exercise.[2] At the initiation of exercise, "central command" from higher brain centers leads to an immediate increase in heart rate and output as well as in blood pressure and respiration.

NEUROLOGIC CAUSES OF POSTURAL HYPOTENSION

Central Lesions

A variety of brainstem lesions can impair autonomic function and affect control of the blood pressure, including syringobulbia and posterior fossa tumors. Chiari malformation with tonsillar herniation may lead to syncopal episodes. Impairment in Wernicke encephalopathy may relate to central or peripheral involvement.

The extent to which cardiovascular reflex function is impaired in *Parkinson disease* is disputed. Many patients with Parkinson disease have postural hypotension from cardiac (especially left ventricular) and extracardiac sympathetic denervation. In such patients, responses to the Valsalva maneuver are also abnormal.[3] Other dysautonomic symptoms, such as disturbances of bladder or gastrointestinal function, and excessive salivation, are relatively common.

The findings in certain *other disorders with parkinsonian features* (e.g., multiple system atrophy, olivopontocerebellar atrophy, and striatonigral degeneration) are discussed later. Postural hypotension may also occur in diffuse Lewy body disease. Mild dysautonomic features may occur late in the course of progressive supranuclear palsy, but cardiovascular reflexes are usually preserved or show only minor abnormalities of dubious significance.

A variety of dysautonomic symptoms may occur in *Huntington disease*, but any abnormalities of blood pressure regulation are usually mild and subclinical, except when related to neuroleptic medication taken for chorea or behavioral disturbances. Postural hypotension or other disturbances of cardiovascular autonomic function occur occasionally in patients with *multiple sclerosis*, but disturbances of bladder and bowel function are much more common dysautonomic features of that disorder. *Wallenberg syndrome* or bilateral brainstem strokes may lead to bradycardia and hypotension that may exacerbate the underlying neurologic problem.

Spinal Injury

The autonomic consequences of spinal cord injuries depend on the level and severity of the lesion. In quadriplegic patients, the period of spinal shock that follows injury is associated with a dysautonomia in which the resting blood pressure and heart rate are typically low and postural hypotension is marked. This mandates that the patient be kept flat, without elevation of the head of the bed, and that any loss of blood volume be avoided or treated vigorously.

A few weeks after transection of the cervical cord, activity returns to the isolated spinal segment, but the brain is no longer able to control the sympathetic nervous system. Loss of regulation during postural change leads to orthostatic hypotension, whereas overactivity occurs if spinal sympathetic reflexes are activated and leads to the syndrome of *autonomic hyperreflexia*. This occurs with usually complete cervical or high thoracic lesions. It is characterized by episodic hypertension, bradycardia, headache, and hyperhidrosis above the level of the lesion, with pallor and piloerection distal to it. Anxiety, confusion, nasal congestion, and facial flushing may also occur. Treatment of this syndrome thus requires avoidance of stimuli that activate spinal sympathetic reflexes (e.g., a distended bladder), elevation of the head of the bed, and, if necessary, use of short-acting antihypertensive agents such as calcium-channel blockers. In general, spinal cord transection produces postural hypotension if the lesion is above about the T6 level. Intramedullary and extramedullary tumors, transverse myelitis, and syringomyelia involving the cord above T6 may also produce dysautonomia.

Root and Peripheral Nerve Lesions

HEREDITARY DISORDERS

Primary amyloidosis and familial amyloid polyneuropathy of Portuguese type (FAP type 1) are often accompanied by dysautonomia consequent to the loss of predominantly unmyelinated and small myelinated peripheral fibers and of cells in the intermediolateral columns of the spinal cord. Postural hypotension and impotence are early manifestations; episodic constipation and diarrhea, distal anhidrosis, impotence, urinary retention, and cardiac arrhythmias may also be conjoined. Tests of sympathetic and parasympathetic function are typically abnormal.

In Fabry disease, disturbed sweating, reduced saliva and tear production, impaired pupillary responses, and gastrointestinal symptoms are common, but postural hypotension does not usually occur, and postural cardiovascular reflexes are normal or only mildly abnormal.

Autonomic involvement may occur in a variety of other hereditary polyneuropathies and in acute porphyria. In familial dysautonomia, or Riley—Day syndrome, many parts of the nervous system are affected. Presentation during infancy may be with inability to suck, but episodic vomiting, recurrent pulmonary infections, hypertension, tachycardia, and diaphoresis occur, especially after 3 years of age. There may also be emotional outbursts, difficulty in swallowing, hypothermia or hyperthermia, poor flow of tears, postural hypotension, and syncope. Sensory abnormalities include impaired pain and temperature appreciation, and the tendon reflexes are depressed. The tongue is smooth and lacks fungiform papillae. Cardiac arrest may occur on tracheal intubation. Treatment is essentially supportive. Postural hypotension usually is not a feature of the other hereditary sensory and autonomic neuropathies, whereas sudomotor function is often markedly impaired.

Autonomic symptoms or signs may occur in patients with hereditary motor and sensory neuropathy type 1, and abnormal vascular reflex responses may be present. Postural hypotension is usually not a conspicuous feature of the disorder.

METABOLIC DISORDERS

Autonomic involvement is particularly frequent in diabetic neuropathy, although usually relatively mild in severity; indeed, diabetes is the most common cause of autonomic neuropathy in the more developed countries. Postural hypotension occurs in approximately 25 percent of patients with diabetic neuropathy. In addition to postural lightheadedness, the dysautonomia of diabetes may be manifest by impotence, postprandial bloating, early satiety, gastrointestinal motility disturbances, abnormalities of bladder control, and alterations of sweating. Cardiac vagal control is usually impaired early, before the development of postural hypotension; the quantitative sudomotor axon reflex test is commonly abnormal and indicates involvement of distal postganglionic sympathetic fibers.

Autonomic dysfunction with abnormal cardiovascular responses occurs in some patients with chronic renal failure on intermittent hemodialysis, but the site of autonomic involvement is unclear. Vitamin B_{12} deficiency may lead to autonomic neuropathy and postural hypotension that improves or resolves completely after vitamin supplementation.

The presence of autonomic neuropathy in patients with chronic alcoholism has been correlated with nutritional status. The cardiovascular responses to various maneuvers are abnormal, reflecting both sympathetic and parasympathetic involvement, but despite this there is often no excessive decline in blood pressure on standing,

INFECTIOUS, INFLAMMATORY, AND IMMUNE-MEDIATED DISORDERS

Postural hypotension may occur in patients with tabes dorsalis because of interruption of circulatory reflexes. Autonomic involvement, with impairment of sweating and cardiovascular responses, occurs in leprosy, sometimes without conspicuous features of peripheral nerve involvement, and also in patients with human immunodeficiency virus infection or Chagas disease.

Autonomic involvement in Guillain—Barré syndrome is usually mild, but paroxysmal cardiac arrhythmias or asystole or episodic hypertension may lead to a fatal outcome. Postural hypotension is common. It has a number of possible causes including inactivity and bed rest, baroreceptor deafferentation, efferent sympathetic denervation, hypovolemia, cardiac abnormalities, or some combination of these and other factors. The severity of autonomic involvement in Guillain—Barré syndrome is not related to the degree of sensory or motor disturbance, and a wide variety of autonomic abnormalities is found if patients are studied in detail. The hypertensive episodes may relate to catecholamine supersensitivity or denervation of baroreceptors. Treatment of Guillain—Barré syndrome is by supportive measures or with plasmapheresis or intravenous immunoglobulin therapy depending on disease severity. Patients with autonomic instability require close observation and management in an intensive care unit. Further aspects of treatment are given on p. 141. Curiously, postural hypotension is uncommon in chronic inflammatory demyelinating polyneuropathy, although mild impairment may be found in many patients on tests of autonomic function.

Autonomic neuropathy of acute or subacute onset, possibly on an autoimmune basis, sometimes occurs as a monophasic disorder in isolation or with associated sensory or motor involvement. It has occurred in the context of antecedent viral infections, malignancy, Hodgkin disease, infectious mononucleosis, ulcerative colitis, celiac disease, and certain connective tissue diseases. In approximately 50 percent of patients, high titers of ganglionic acetylcholine receptor (AChR) antibody are found. In patients with a paraneoplastic etiology, other autoantibodies may be present, including antineuronal nuclear antibody 1 (ANNA-1 or anti-Hu) or 2 (ANNA-2), Purkinje cell antibody 2 (PCA-2), collapsin response-mediator protein 5 antibody (CRMP5), and *N*-methyl-D-aspartate (NMDA) receptor antibody. The presence of such antibodies may suggest the likely site of an underlying primary tumor. Both sympathetic and parasympathetic fibers are usually involved, leading to marked postural hypotension accompanied by a fixed heart rate, anhidrosis or hypohidrosis, heat intolerance, sphincter disturbances, gastroparesis, ileus, and dryness of the eyes and mouth, but occasionally abnormalities are confined to postganglionic cholinergic neurons (acute cholinergic neuropathy), in which case postural hypotension does not occur. Pure adrenergic neuropathy has also been described. Autonomic function tests reflect the clinical findings. Nerve conduction study results are typically normal, but sensory abnormalities are sometimes found. Treatment is supportive; immunomodulating therapy may have a role in those with severe disease. Paraneoplastic dysautonomia may remit if the underlying malignancy is treated. The prognosis of patients with acute or subacute autonomic neuropathies is guarded: approximately one-third of patients do well, but the remainder either fail to improve or are left with a major residual deficit, including marked postural hypotension.

Symptoms of autonomic impairment, including postural hypotension, may also be a presenting feature of systemic autoimmune disorders.

IATROGENIC DISORDERS

Iatrogenic postural hypotension is common in the elderly and relates most often to the use of antihypertensive agents or diuretics. Iatrogenic polyneuropathies may be responsible in other instances, however. For example, postural hypotension may be conspicuous in patients with the neuropathy caused by perhexiline maleate, cisplatin, paclitaxel (Taxol), vinca alkaloids, or amiodarone.

Toxic Exposure

Autonomic dysfunction may result from occupational or other exposure to certain neurotoxins but does not usually lead to postural hypotension. Long-term occupational exposure to a mixture of organic solvents may cause subtle disturbances of peripheral parasympathetic nerves as well as sensorimotor peripheral neuropathies, as reflected by cardiovascular reflex studies, but reports of autonomic involvement in this context are few. Intentional inhalation of *n*-hexane or methyl-*n*-butyl-ketone for recreational purposes may lead to a rapidly progressive neuropathy with associated postural hypotension. Acrylamide neuropathy is usually accompanied by hyperhidrosis and cold, cyanotic extremities; experimental studies in animals reveal baroreceptor dysfunction, but the clinical significance of this in humans is unclear. A variety of autonomic symptoms (including tachycardia, hypertension, and disturbances of sweating) may occur with thallium, arsenic, or mercury poisoning, but postural hypotension is not usually a feature.

The rodenticide *N*-3-pyridylmethyl-*N*′-*p*-nitrophenyl urea (Vacor) has caused severe dysautonomia with disabling postural hypotension, as well as sensorimotor peripheral neuropathy and encephalopathic states. Symptoms reflecting autonomic dysfunction (anorexia, nausea, hyperhidrosis, and tachycardia) have been associated with cumulative exposure to moderate levels of pesticides, particularly organophosphate or organochlorine insecticides, regardless of recent exposure or history of poisoning[4] but whether postural hypotension occurs is unclear.

Primary Degeneration of the Autonomic Nervous System

Postural hypotension resulting from primary degeneration of the autonomic nervous system is well described. The postural hypotension is often exacerbated postprandially, and the normal circadian rhythm is reversed so that the blood pressure is highest at night and lowest in the morning. In addition, blood pressure typically declines with activity rather than increasing as in normal subjects. Other symptoms of dysautonomia in these patients include erectile dysfunction, disturbances of bladder and bowel function, impaired thermoregulatory sweating, and xerostomia. Two distinct groups of patients are now recognized. In one, primary or *pure autonomic failure* (PAF) leads to idiopathic orthostatic hypotension and other evidence of dysautonomia without peripheral neuropathy or CNS involvement. In the other, autonomic failure is associated with more widespread neurologic degeneration (i.e., with evidence of *multiple system atrophy* or MSA) such that there may be clinical features of parkinsonism or striatonigral degeneration (MSA-P), and often of more widespread neurologic lesions as well. A disorder similar to olivopontocerebellar atrophy may also occur (MSA-C). The autonomic deficit may precede the somatic neurologic one, or vice versa, but within a short period there is clinical evidence of both. Occasionally there is a family history of dysautonomia.

The time course and pattern of the dysautonomia reportedly differ between these two disorders, both of which are synucleinopathies. In PAF, syncope and sudomotor dysfunction may precede the onset of constipation, bladder dysfunction, or respiratory disturbances whereas in MSA, urinary complaints occur early and are then followed by abnormalities of sweating or by postural hypotension. Patients with PAF have a slower functional deterioration and a better prognosis. The ingestion of water temporarily increases the seated blood pressure by uncertain mechanisms in patients with chronic autonomic failure. This occurs earlier in PAF than MSA, perhaps reflecting differing lesion sites in these two disorders.

Most patients with PAF have imaging and neuropathologic evidence of cardiac sympathetic denervation, whereas such innervation generally is intact in MSA because there is loss of central rather than peripheral autonomic neurons.[3] In patients of both groups, plasma renin activity is usually subnormal. There are, however, a number of reported pharmacologic differences between them. Patients with PAF have low plasma norepinephrine levels when lying down, and these levels fail to increase appropriately on standing; they also have a lower threshold for the pressor response to infused norepinephrine. The increase in plasma norepinephrine level in response to tyramine (see p. 138) is significantly less than in normal subjects or patients with MSA.[5] Extensive cell loss occurs in the intermediolateral cell columns of the thoracic cord, and the autonomic dysfunction has been attributed primarily to loss of these preganglionic sympathetic neurons. However, the pharmacologic studies described previously indicate that loss of postganglionic noradrenergic neurons also occurs, and norepinephrine may be depleted from sympathetic nerve endings.

By contrast, in MSA, in which lesions are situated at multiple sites in the CNS, circulating norepinephrine levels are normal, suggesting that peripheral sympathetic neurons are intact, but plasma norepinephrine fails to increase appropriately with standing, implying that these neurons have not been activated.[5] There is also an exaggerated pressor response to infused norepinephrine, but only patients with idiopathic orthostatic hypotension show a shift to the left in their dose—response curve, reflecting true adrenergic receptor supersensitivity.[5]

Central catecholamine deficiency in these disorders is reflected by the levels in the cerebrospinal fluid of dihydroxyphenylacetic acid (a neuronal metabolite of dopamine), which are lower in patients with MSA or PAF than normal subjects, as also is dihydroxyphenylglycol, a metabolite of norepinephrine.

Endogenous arginine vasopressin is a powerful vasoconstrictor; it also acts on the kidney to control urinary concentrating mechanisms. The cardiovascular responses usually associated with arginine vasopressin are reduced cardiac output, heart rate, and plasma renin activity and increased vascular resistance and blood pressure. Arginine vasopressin helps maintain arterial pressure in certain hypotensive situations such as hemorrhage or volume depletion, but increased levels of arginine vasopressin do not normally affect the blood pressure significantly because the acute vasoconstrictor effects are buffered by the baroreceptor reflex. The chronic effects of vasopressin on renal function do not produce sustained retention of sodium and water, and so produce only minimal changes in mean arterial pressure.

Vasopressin release is influenced by the plasma's osmotic pressure and by the activity of vascular stretch receptors. In normal people, plasma arginine vasopressin increases in response to standing, presumably because a decrease in venous return influences afferent activity from these stretch receptors. In patients with PAF or with MSA, plasma levels similar to control values are found in the horizontal position, but the postural increase is markedly attenuated.

Miscellaneous Disorders

Patients with *Holmes—Adie syndrome* may present with or develop postural hypotension or abnormalities of thermoregulatory sweating. Postural hypotension may occur in *botulism*; however, blurred vision, dry mouth, and constipation are much more common autonomic manifestations. In rare instances, it relates to excessive amounts of endogenous bradykinin (a vasodilator) or a congenital defect of norepinephrine release. In patients with *dopamine β-hydroxylase* *deficiency*, norepinephrine and epinephrine cannot be synthesized, and dopamine is released from central and peripheral adrenergic nerve terminals. Severe postural hypotension is accompanied by other autonomic disturbances in association with absent norepinephrine and excessive dopamine levels in the plasma.

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

Orthostatic symptoms may develop in association with a significant and sustained tachycardia within 10 minutes of standing or head-up tilt, but in the absence of postural hypotension or an autonomic neuropathy. A significant tachycardia is defined as an increase in heart rate of 30 beats per minute or more, or a heart rate of at least 120 beats per minute. The designation *postural orthostatic tachycardia syndrome* (POTS) is applied to this disorder, which is more common in women than men and tends to occur in patients between 20 and 50 years of age, with about half the patients developing symptoms in adolescence. The syndrome may have an enormous impact on patients' quality of life.

Symptoms on standing include tremulousness, lightheadedness, palpitations, visual disturbances, "brain fog," generalized weakness, daytime somnolence, fatigue, anxiety, hyperventilation, nausea, postprandial bloating, and sweating, and may occur cyclically. Thus, orthostatic symptoms are accompanied by symptoms of sympathetic activation.

The diagnosis is suggested by the history and examination findings and confirmed by recording the heart rate and blood pressure on standing for 10 minutes after the patient has been lying supine for 10 minutes. Measurements are made at 1, 3, 5, and 10 minutes after standing. Testing is best performed in the morning, when orthostatic tachycardia is typically more pronounced. Other medical problems that may cause a tachycardia (such as pain, infection, anemia, hypovolemia, hyperthyroidism, and various medications) must be excluded before POTS is diagnosed. More detailed testing of autonomic function is sometimes performed in selected patients but is generally not required unless doubt exists about the diagnosis, it is wished to define the subtype of POTS, or the response to treatment is disappointing. Further investigations may be required to explore the basis of other symptoms.

POTS has been subdivided into various overlapping subtypes depending on clinical manifestations and mechanisms presumed to be involved. The pathophysiologic basis of POTS is uncertain and probably multifactorial, but cardiac deconditioning (characterized by physiologic cardiac atrophy and hypovolemia) is held to be a factor. Prolonged bedrest can lead to orthostatic tachycardia and intolerance in previously healthy subjects. POTS has been related also to inadequate venous return to the heart during standing. Specifically, peripheral vasoconstriction is impaired by peripheral sympathetic denervation, leading to venous pooling in the legs on standing and to a compensatory tachycardia. Denervation is evidenced by impaired sweating in the legs or a reduced density of intraepidermal nerve fibers on skin biopsy in many of these patients, who are deemed to have "neuropathic POTS." In other instances, patients with ("hyperadrenergic") POTS may have an exaggerated sympathetic response to standing, with markedly elevated levels of plasma norepinephrine that cause the orthostatic tachycardia. The increased norepinephrine level may relate, in turn, to impaired synaptic clearance by the norepinephrine transporter (NET) either on a genetic basis or because of medications being taken, such as certain antidepressants. Other postulated mechanisms for POTS involve impaired brainstem regulation; immune system dysfunction; hormonal factors; hypovolemia, perhaps from impaired function of the renin-angiotensin system ("volume dysregulation POTS"); and excessive mast cell activation leading to inappropriate release of histamine during physical activity. Psychologic mechanisms have also been invoked. The evidence for these various mechanisms is incomplete, and different mechanisms or combinations of mechanisms may be involved in different patients.

POTS can be associated with certain other disorders, especially joint hypermobility syndrome but also migraine, concussion, chronic fatigue, fibromyalgia, diabetes, paraneoplastic syndrome, amyloidosis, sarcoidosis, alcoholism, lupus, Sjögren syndrome, and heavy metal intoxication, and it may follow pregnancy, surgery, trauma, chemotherapy (especially with vinca alkaloids), vaccinations, or viral infections. It may also occur in association with mitral valve prolapse or a more specific dysautonomia.

The optimal therapy for the disorder is not clear, but treatment may include volume repletion, a high-salt diet and copious fluids, postural and psychophysiologic training, and a 3-month, graduated exercise program. These nonpharmacologic measures—and education of the patient—are often very effective in alleviating symptoms. Waist-high compression stockings may help, especially in patients with low blood pressure. If pharmacologic measures are needed, there are several options. If palpitations are the most conspicuous symptom, a β-blocking agent (e.g., propranolol 10 to 40 mg three times daily) may be used. Phenobarbital (15 mg in the morning, 60 mg at night) or clonidine (0.2 mg twice daily) is sometimes helpful for patients with such hyperadrenergic POTS. If the blood pressure is low and symptoms such as lightheadedness predominate, midodrine (2.5 to 10 mg three times daily) or fludrocortisone (0.1 to 0.2 mg daily) may be prescribed, and pyridostigmine (30 to 60 mg three times daily) is also worthy of trial. In other instances, norepinephrine and serotonin reuptake inhibitors may be worthwhile.

The long-term prognosis is not clear but approximately 50 percent of patients recover within 3 years.

SYMPTOMS OF DYSAUTONOMIA

General

Postural hypotension is usually the most disabling feature of autonomic failure. It leads to symptoms on or shortly after standing; they are relieved by sitting or lying down, and do not occur in the supine position. Such symptoms reflect cerebral hypoperfusion and include faintness, lightheadedness, blurred vision, and syncope. They may be particularly troublesome after exercise or a heavy meal (particularly a meal rich in carbohydrates) or in the morning when the blood pressure tends to be at its lowest (in contrast to healthy subjects). However, in some patients, marked postural hypotension may be clinically asymptomatic or may be accompanied by symptoms not usually regarded as suggestive of postural hypotension, such as nausea, breathlessness, heaviness or weakness of the limbs, episodic confusion, impaired concentration, falling, staggering, headache and neck pain, neck and shoulder discomfort, and generalized weakness. Constipation may precipitate syncopal attacks during straining. Symptoms may also worsen in the heat because of vasodilatation and volume loss due to sweating. The symptoms of idiopathic POTS (discussed earlier) may be mistakenly attributed to postural hypotension, but occur without a significant decrease in blood pressure. Other causes, such as hypoglycemia, cardiac arrhythmias, or transient ischemic attacks, must be excluded if symptoms develop with the patient supine.

Erectile dysfunction is a common initial symptom of autonomic dysfunction in men, often preceding other symptoms by several months or years. Bladder involvement may manifest by urinary frequency, urgency, incontinence, retention, and increased residual urine; urinary infections and renal calculi may occur in some patients with urinary stasis. Gastrointestinal dysfunction may lead to early satiety, constipation, fecal incontinence, and diarrhea. Thermoregulatory sweating may be impaired. Pupillary abnormalities include Horner syndrome and anisocoria. Lacrimal dysfunction may lead to inadequate or excessive production of tears. Other symptoms of dysautonomia include night blindness, nasal congestion, and, sometimes, supine hypertension. Vocal abnormalities and respiratory disturbances (especially involuntary inspiratory gasps, cluster breathing, airway obstruction, and sleep apnea) sometimes occur, especially in patients with multiple system atrophy.

Syncope

Syncope refers to a sudden, transient loss of consciousness due to diffuse cerebral hypoperfusion or hypoxia. It is usually associated with flaccidity, but a generalized increase in muscle tone sometimes occurs with continuing cerebral ischemia/hypoxia, and there may be arrhythmic transient motor activity as well. Postictal confusion is usually brief (less than 30 seconds) when it occurs at all, unlike the marked postictal confusion that often follows a convulsion. Syncope has been divided into syncope from postural hypotension, reflex (i.e., neurally mediated) syncope, and cardiac syncope (arrhythmic or associated with structural cardiac disease).[6]

POSTURAL HYPOTENSION

In patients with postural hypotension due to autonomic dysfunction, there is a decline in blood pressure on standing, without adequate compensatory change in total peripheral resistance or heart rate, and syncope may result. When postural hypotension occurs because of one of the non-neurologic causes discussed earlier, it may also lead to syncope if autonomically mediated compensatory mechanisms fail to limit the decline in blood pressure. In neurogenic postural hypotension, a failure of autonomic activation may result in a lack of premonitory symptoms such as tachycardia, nausea, or diaphoresis.

Neurally Mediated Syncope

During *vasovagal syncope*, there is an initial increase in heart rate, blood pressure, total peripheral resistance, and cardiac output, followed by peripheral vasodilatation, increased blood flow to the muscles, decreased heart rate, and a decrease in venous return to the heart. Blood pressure falls owing to failure to increase the heart rate and cardiac output sufficiently, a decrease in systemic vascular resistance, or both. The decline in heart rate and cardiac contractility constitute the cardioinhibitory response. The vasodilatation and decline in systemic vascular resistance constitute the vasodepressor response. These various phenomena have been related to Bezold–Jarisch reflexes arising from cardiac sensory receptors and subserved by vagal afferent fibers, perhaps as a consequence of a decrease of central blood volume and decreased ventricular filling.[6] Recordings from nerve fibers reveal that impulse traffic ceases in the sympathetic outflow to skeletal muscle during syncope and gradually builds up again over the following 5 minutes or so.[7] Withdrawal of sympathetically mediated vasoconstriction may underlie the profound systemic vasodilatation that leads to hypotension and subsequent syncope, but other mechanisms are probably also involved in the peripheral vasodilation.[7]

Syncope of this sort may be precipitated by pain, fear, emotional reactions, injury, and surgical manipulation. It may occur in association with missed meals, heat, or crowds; it usually occurs while subjects are standing. Warning symptoms include weakness, sweating, pallor, nausea, yawning, sighing, hyperventilation, blurred vision, impaired external awareness, and dilatation of pupils. Lying down or squatting at this time may abort actual loss of consciousness.

Deglutition syncope is characterized by syncope precipitated by swallowing. In such instances, there may be associated esophageal disorders. The syncope has usually been attributed to atrioventricular heart block or cardiac arrhythmia. It is presumed that the prime factor is clinical or subclinical disease of the conducting system of the heart and that disturbances of cardiac rhythm are then triggered by reflexes originating in the esophagus. A pacemaker may prevent further episodes.

Micturition syncope occurs after urination, particularly when the patient has arisen from bed at night. It may relate to sudden release of the reflex vasoconstriction elicited by a full bladder. Assumption of the upright posture, the peripheral vasodilatation resulting from the warmth of the bed, and, particularly in elderly men, straining to micturate may also contribute to the drop in blood pressure. Occasionally, syncope occurs in response to cardiac dysrhythmia induced by a full bladder before micturition.

Carotid sinus syncope may be provoked by neck-turning or a tight collar in susceptible subjects. Certain drugs have also been shown to predispose toward it, especially propranolol, digitalis, and α-methyldopa, and it may occur during internal carotid angioplasty. A hypersensitive carotid sinus reflex is defined by a slowing in heart rate of more than 50 percent or a decline in systolic pressure by more than 40 mmHg during carotid sinus massage. However, less than 50 percent of patients with carotid hypersensitivity have syncope as a result. Conversely, in many patients with syncope of unidentifiable cause, the carotid sinus syndrome may have been overlooked.

The *Valsalva maneuver* may lead to syncope, as when syncope occurs during vigorous coughing or straining at stool as a result of the reduced cardiac output and the peripheral vasodilatation caused by the high intrathoracic pressure. Cerebral perfusion may also be reduced by an increase in intracranial pressure.

Cardiac Syncope

As discussed earlier, postural hypotension may have a cardiac basis. In addition, disturbances of cardiac rhythm may lead to sudden loss of consciousness, regardless of the position of the body (Adams–Stokes attacks). Further discussion of this topic is provided in Chapter 5. Exertional syncope suggests obstructive valvular disease or a right-to-left shunt. Coronary artery disease may lead to arrhythmias that cause syncope.

Hyperventilation

Hyperventilation, with consequent hypocapnia and reduced cerebral perfusion, is a common cause of presyncopal symptoms, but actual loss of consciousness is uncommon.

EVALUATION OF AUTONOMIC FUNCTION

After neurologic, cardiologic, and metabolic causes of syncope have been excluded, a number of patients remain in whom the diagnosis is unclear. The utility of autonomic studies in these circumstances was examined by Mathias and colleagues.[8] They found that screening autonomic function tests revealed postural hypotension and confirmed chronic autonomic failure in 5 percent, and neurally mediated syncope was diagnosed in 43.5 percent based on clinical features and autonomic studies. Thus, in recurrent syncope or presyncope, autonomic studies are worthwhile as they may clarify the diagnosis. In patients with unexplained syncope, the implantable loop recorder is an important diagnostic tool that may clarify the underlying pathophysiology.

Postural Change in Blood Pressure

In investigating patients with suspected autonomic dysfunction or postural hypotension, the blood pressure should be measured with the patient supine for at least 2 (preferably 10) minutes. The patient then stands up, and the blood pressure is measured again after 5 to 10 seconds, and again after 1, 2, 3, and 5 minutes. There is normally an increase in pulse rate on standing, but the pulse rate may not change if there is already a high resting pulse or in patients with dysautonomia; furthermore, the change in heart rate may be blunted in the elderly. As for the blood pressure, there is normally a slight decline in systolic pressure, whereas diastolic pressure increases slightly. The response of the blood pressure is regarded as abnormal if systolic pressure decreases by at least 20 mmHg or diastolic pressure by 10 mmHg on standing. In some instances, postural hypotension develops only after exercise or a meal; it is therefore worthwhile to record the postactivity and postprandial blood pressure if clinically feasible. It may be necessary to record the blood pressure on a number of occasions before the diagnosis of postural hypotension can be confirmed. Normal responses do not exclude postural hypotension as a cause of symptoms. In other instances, prolonged tilt (for up to 60 minutes) on a tilt table may be required to detect abnormalities.

Blood pressure normally is higher in the day, declines at night, and rises prior to awakening. Patients with postural hypotension may show a circadian trend in blood pressure that is the reverse of normal subjects, with the highest pressures found at night and the lowest in the morning. Further, postural hypotension may be more severe in the morning after prolonged nocturnal recumbency due to a decline in stroke volume and cardiac output, resulting not only from nocturnal polyuria but also from a redistribution of body fluid. Such temporal variation in blood pressure implies that physiologic testing should be carried out at a standard time of day, especially if comparative studies are to be performed, and potentially harmful hypertension in response to treatment should be looked for especially during the early part of the night.

Tilt-Table Testing

The effect of postural change on blood pressure can be evaluated more accurately if the blood pressure is measured using an intra-arterial cannula or a noninvasive plethysmographic device with the patient resting quietly on a tilt table. Measurements are made continuously while the patient lies supine for at least 10 minutes and is then maintained at a 60- or 70-degree head-up tilt for up to 60 minutes, depending on the reason for the study. Testing on a tilt table permits longer monitoring of hemodynamic responses than does active standing. The response to head-up tilt differs from that obtained by standing because the venous return to the heart is not aided as much by contraction of leg and abdominal muscles, and thus there is greater peripheral pooling of blood. Compared to passive tilt, active standing leads to a greater but transient decline in blood pressure, a larger increase in heart rate, a greater decline in total peripheral resistance, and a more marked increase in cardiac output during the first 30 seconds.[9]

Tilt-table testing is performed to determine whether patients have postural hypotension and—if so—whether this is the cause of postural symptoms. It is helpful in the diagnosis of POTS and of delayed postural hypotension (i.e., hypotension that occurs after standing for 3 minutes or longer), and in distinguishing between neurogenic and other causes of postural hypotension, between convulsive syncope and epilepsy, and between syncope and psychogenic attacks.[9] With head-up tilt, blood pressure generally falls rapidly and does not recover until the horizontal position is restored.

Postural Change in Heart Rate

A simple, noninvasive test of autonomic function consists of evaluating the response in heart rate to change from a recumbent to a standing position.

There is typically a rapid increase in heart rate that is maximal at approximately the fifteenth beat after standing, with a subsequent slowing from the initial tachycardia (i.e., a relative bradycardia) that is maximal at approximately the thirtieth beat (Fig. 8-3). This response is mediated by the vagus nerve. For testing purposes, the R-R interval at beats 15 and 30 after standing can be measured to give the 30/15 ratio, as reviewed in detail elsewhere. Values greater than 1.03 occur in normal subjects, whereas in diabetic patients with autonomic neuropathy (who typically show only a gradual increase in heart rate), values are 1.00 or less. Some prefer to measure the ratio of the absolute maximum to absolute minimum heart rate after standing, which may not coincide with the heart rates at beats 15 and 30. This test does not depend on the resting heart rate and correlates well with the Valsalva ratio and the beat-to-beat variation in heart rate, described later. The value for the 30/15 ratio declines with age in normal subjects.

In some patients, an excessive and sustained tachycardia develops in response to standing or head-up tilt, without a significant drop in blood pressure. A prolonged tilt (for up to 60 minutes) may be necessary to elicit the abnormality. The mechanisms underlying this postural tachycardia have not been clearly established.

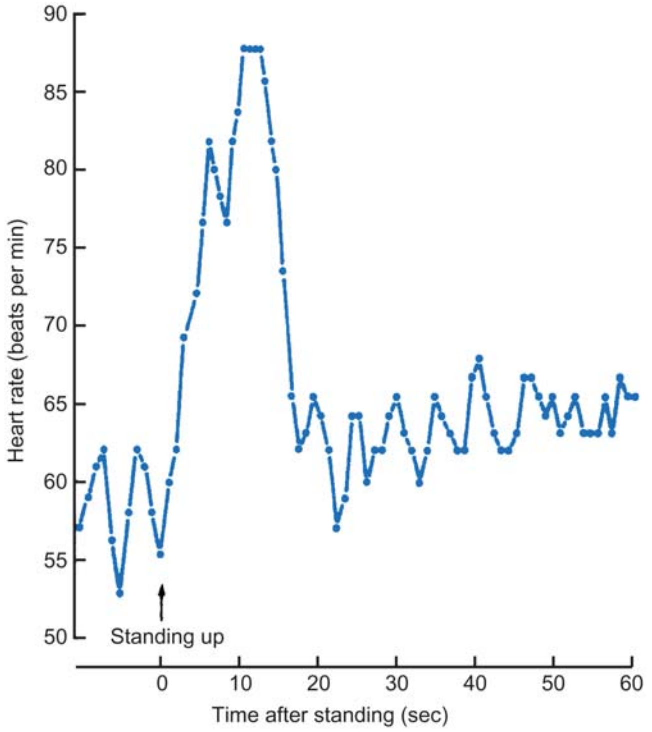

FIGURE 8-3 ■ Heart rate responses to standing in a normal subject. Immediately on standing, there is a rapid increase in heart rate that is maximal at approximately the fifteenth beat after standing.

Valsalva Maneuver

The Valsalva maneuver consists of a forced expiration maintained for at least 10 seconds (preferably 15 seconds) against a closed glottis after a full inspiration. Intrathoracic pressure should be increased by 30 to 40 mmHg. Clinically, this can be ensured by requiring the patient to blow into a mouthpiece connected to a manometer. The response can be recorded with an intra-arterial needle (Fig. 8-4), a noninvasive photoplethysmographic recording device (Finapres), or an electrocardiograph (ECG) (Fig. 8-5).

The cardiovascular response is usually divided into four stages. Stage 1 is characterized by a transient increase in blood pressure at the onset of the forced expiration, reflecting the increased intrathoracic pressure. In stage 2, there is normally a gradual decrease in systolic and diastolic pressures, pulse pressure, and stroke volume for several seconds because of a reduction in venous return to the heart, with an associated reflex tachycardia. Reflex vasoconstriction arrests the decline in blood pressure after about 5 to 7 seconds. Stage 3 occurs when the patient releases the expiratory maneuver and is characterized by a transient fall in the blood pressure because of pooling of blood and expansion of the pulmonary vascular bed with the abrupt decline in intrathoracic pressure. In stage 4, there is an overshoot of the blood pressure above baseline value as a result of the peripheral vasoconstriction, with a compensatory bradycardia.

The Valsalva maneuver is an accurate indicator of baroreceptor reflex sensitivity. Abnormalities are found in patients with dysautonomia (Fig. 8-4) and may consist of loss of the overshoot in systolic blood pressure and compensatory bradycardia in stage 4, a fall in mean blood pressure in stage 2 to less than 50 percent of the previous resting mean pressure, and loss of the tachycardia in stage 2, or a lower heart rate in stage 2 than stage 4. However, abnormalities may also be found in patients with severe congestive heart failure and in those with cardiac lesions other than primary myocardial dysfunction.

If the response is recorded noninvasively using an electrocardiograph, the ratio of the shortest R-R

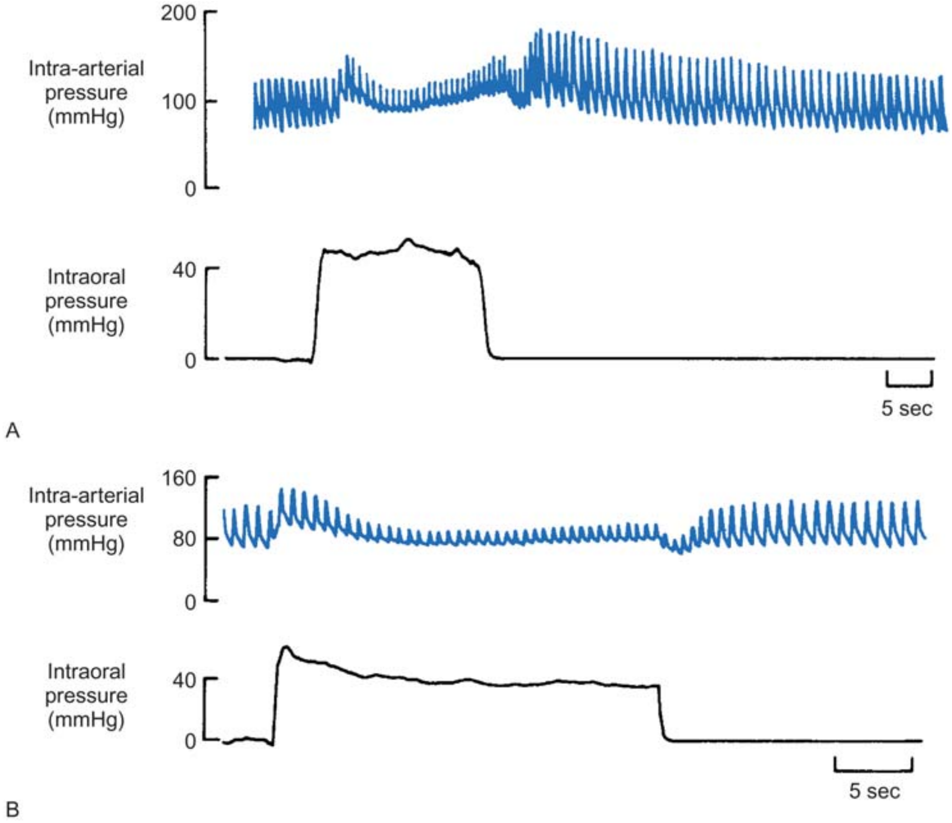

FIGURE 8-4 ■ Cardiovascular responses to the Valsalva maneuver, as recorded with an intra-arterial needle. *A*, Normal response. *B*, Abnormal response in a patient with multiple system atrophy. (From Aminoff MJ: Electromyography in Clinical Practice. 3rd Ed. Churchill Livingstone, New York, 1998, p. 206, with permission.)

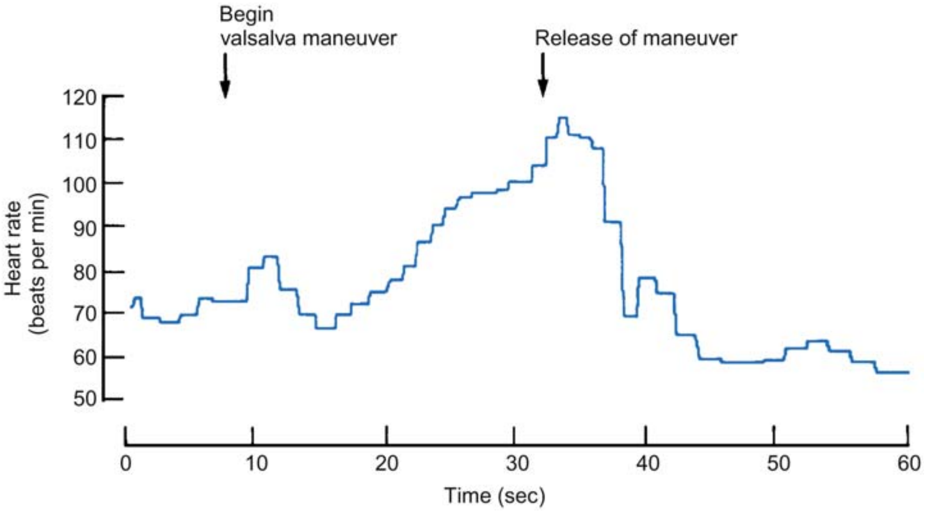

FIGURE 8-5 ■ Valsalva maneuver as recorded using an electrocardiograph (ECG) or heart rate monitor in a normal subject. The tachycardia that occurs during the forced expiratory maneuver is clearly evident, as is the compensatory bradycardia that occurs when the maneuver is released.

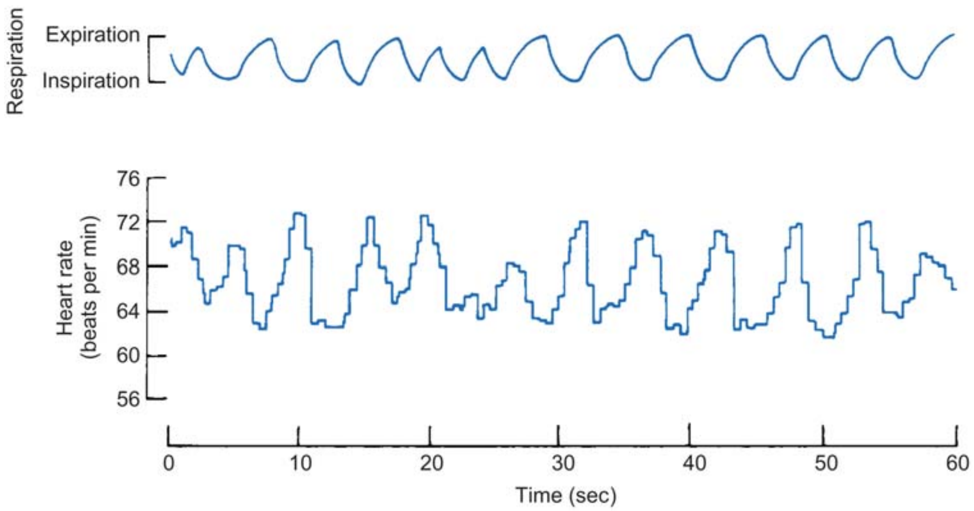

FIGURE 8-6 ■ Normal variation in heart rate that occurs in response to deep breathing.

interval (the tachycardia) during the maneuver to the longest R-R interval (bradycardia) after it is determined and expressed as the Valsalva ratio. In early studies, a value of 1.1 or less was arbitrarily defined as an abnormal response, 1.21 or greater as a normal response, and 1.11 to 1.20 as borderline. Using such criteria, the Valsalva maneuver was found to be abnormal in about 60 percent of diabetic patients with symptoms and signs suggestive of autonomic neuropathy. When more generous criteria for abnormality were used, with a lower limit for normal of 1.50, the value was abnormal in 86 percent of these patients, and such an abnormality correlated well with the presence of a significant postural drop in blood pressure. Subsequent studies have shown that age- and gender-based normal values should be used.

Other Cardiovascular Responses

Other cardiovascular responses can also be measured noninvasively (e.g., the beat-to-beat variation in heart rate and the heart rate responses to deep breathing and sustained hand grip). Such tests of parasympathetic function appear to give abnormal results more often and earlier than tests of sympathetic efferent function (blood pressure response to change in posture and isometric exercise), at least with the dysautonomia that occurs in diabetes. Reduced cardiovascular autonomic function, as reflected by heart rate variability, is associated with an increased risk of silent myocardial ischemia and death in patients with diabetic autonomic neuropathy.

A particularly useful test is to measure the heart rate variation during deep breathing (Fig. 8-6). In normal subjects, there is considerable heart rate variation, which is accentuated during deep breathing. This variation is reduced or absent in diabetic patients with autonomic neuropathy. The optimal breathing rate for this test is six breaths per minute (i.e., inspiration = expiration = 5 seconds). Heart rate variation scores can be calculated by measuring the difference between the maximal and minimal heart rates in inspiration and expiration, taking the average from 10 breaths in and 10 breaths out. Normal subjects usually have a score greater than 9, and autonomic neuropathy is probably absent if scores greater than 12 are obtained; the normal range, however, is age dependent. Thus, heart rate variability declines with age in normal subjects. The use of a single normal value regardless of age may therefore limit the utility of the test. Physical fitness, body weight and position, time of testing, and concomitant medication may affect the test results.

An increase in heart rate and blood pressure should also occur in response to startle, such as occurs with a sudden loud noise, and to mental stress, as is produced when the patient attempts to subtract 7 serially from 100 while constantly being distracted.

Digital Blood Flow

Blood flow to a finger can be measured by conventional plethysmography or photoplethysmography. A sudden inspiratory gasp causes reflex digital vasoconstriction as a spinal or brainstem reflex, and this is easily measured plethysmographically (Fig. 8-7). The response is impaired or absent in patients with a lesion of the cord or sympathetic efferent pathway, as in peripheral neuropathy or pure autonomic failure. In entrapment neuropathy, such as carpal tunnel syndrome, the vasoconstrictor response may be abolished in fingers supplied by the affected nerve but not in those supplied by other nerves.

Mental stress (e.g., performing mental arithmetic despite distraction) or startle (as from a sudden loud noise) leads to a transient increase in sympathetic vasomotor activity and thus to a reduction in digital blood flow; this can be used to evaluate sympathetic efferent pathways. Normal subjects sometimes have no response to these tests, however, leading to false-positive results.

Cold Pressor Test

In the cold pressor test, one hand is immersed in ice water at 4°C, and this normally produces an increase in systolic pressure of 15 mmHg or more within 1 minute. The afferent pathway involves the spinothalamic tract, and if this tract is intact, the lack of a pressor response suggests a lesion centrally or in the sympathetic efferent pathway. A normal response in a patient with an abnormal Valsalva response and intact pain and temperature sensation suggests an afferent baroreceptor lesion.

Plasma Norepinephrine Level and Infusion

The plasma norepinephrine level can be used as an index of sympathetic activity. In normal subjects the level doubles within 5 minutes of standing. In patients with a central dysautonomia such as MSA, plasma norepinephrine levels are normal, whereas in PAF they are low. Perhaps of greater value, the blood pressure can be measured in response to intravenous infusion of norepinephrine at several dose rates up to 20 μg/min.[5] In this way, a dose—response curve can be constructed. In normal subjects, it is usually necessary to administer 15 to 20 μg/min to increase systolic blood pressure to 40 mmHg above baseline. A similar increase in blood pressure results from doses of 5 to 10 μg/min in MSA and less than 2.5 μg/min in patients with PAF.[5]

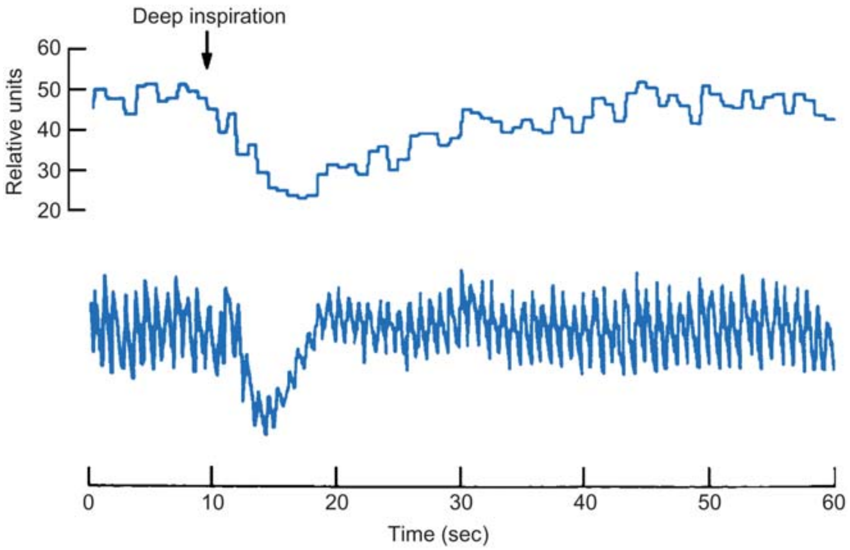

FIGURE 8-7 ▪ Variation in blood volume after a deep inspiration in a normal subject, measured photoplethysmographically by means of an infrared emitter and detector placed on the pad of the index finger. The bottom trace represents the sensor output after it has been amplified by the photoplethysmographic module of a computerized autonomic testing system; it is a function of the absolute blood volume in the finger. Each peak represents a heartbeat, and the amplitude of each wave reflects blood volume in the area about the sensor. The apparent shift of the direct-current signal component is due to the long time constant that is necessary so that signal information is not lost. The relative voltage, representing the amplitude of each pulse, is shown in the upper trace. It is evident in both traces that after the deep inspiration there is a reduction in digital blood flow (i.e., reduced amplitude of the waveforms in the lower trace and a corresponding decline in the upper trace).

Response to Tyramine

Tyramine, an indirectly acting sympathomimetic drug, can be used to test neuronal uptake and release of norepinephrine. Bolus injections ranging from 250 to 6,000 μg are administered and blood pressure is measured at 1-minute intervals. The amount of norepinephrine released into plasma by tyramine can be quantified by obtaining a blood sample shortly after the rise in blood pressure.[5]

Sweat Tests

Cutaneous blood vessels and sweat glands are supplied by sympathetic fibers intermingled in the same fascicles but of different size and conduction velocity. Commonly used tests of sweating are messy and require application of heat, which is time-consuming. A heat cradle placed over the trunk is used to produce an increase of 1°C (from a resting level of 36.5° to 37.0°C) in the oral temperature over the course of 30 to 60 minutes, and the presence of sweat over selected regions of the trunk and limbs is detected by the change in color produced in quinizarine powder, a starch—iodide mixture, or some other indicator powder. The pattern of any impairment of sweating may be helpful in suggesting the underlying cause (Fig. 8-8). For example, impairment is usually distal in the limbs in patients with polyneuropathies. The method does not distinguish preganglionic from postganglionic lesions.

The volume of sweat produced by axon-reflex stimulation either electrically (faradic sweat response) or with parasympathomimetic drugs under specified conditions indicates the state of sudomotor innervation in the tested limb (Fig. 8-9). After a short latent period, sweating occurs in an area that is approximately 4 to 5 cm in diameter about the site of stimulation. The reflex is subserved by sympathetic postganglionic fibers; impulses pass centripetally along these fibers until they reach a branch point and then pass distally again. The receptor involved in the reflex has not been defined. To quantify the volume of sweat, recordings are made of the humidity change of an air stream of defined flow. Such quantitative sudomotor axon reflex testing (QSART) is a sensitive means of assessing postganglionic sympathetic function by using iontophoresed acetylcholine to stimulate the involved receptors; it yields reproducible results but requires sophisticated and expensive equipment. Yet another approach to evaluating postganglionic sympathetic sudomotor function is with the silicone mold technique, in which imprints are made of sweat droplets stimulated by iontophoresed acetylcholine.

Sudomotor function can also be evaluated by measuring changes in skin resistance. With sweating,

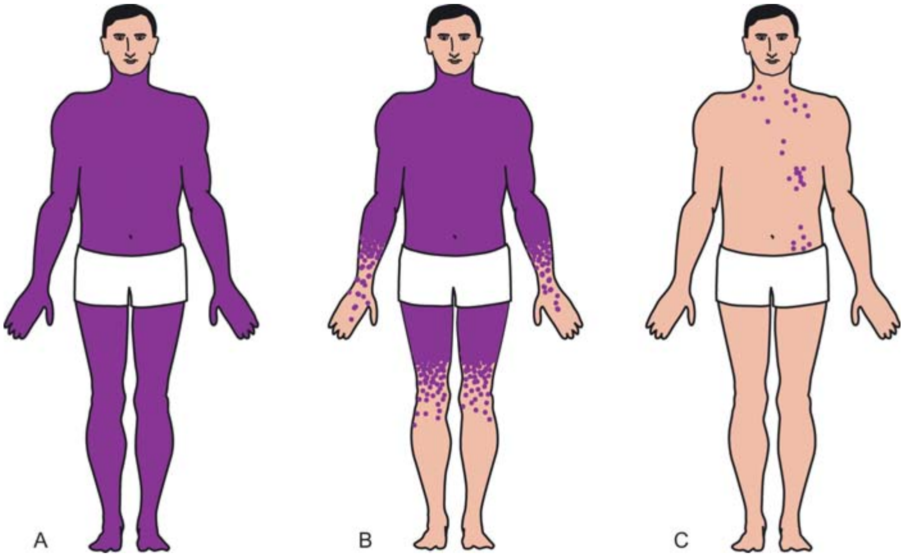

FIGURE 8-8 ■ Thermoregulatory sweat tests. *A*, An increase in body temperature leads normally to sweating over the entire body. An indicator powder becomes discolored (purple) by the moisture. It was not placed on the face and head, so that no discoloration is seen in these regions. *B*, In a patient with a length-dependent neuropathy involving the sudomotor fibers, sweating is absent in a stocking-and-glove-pattern. *C*, A patient with multiple system atrophy and almost complete anhidrosis, showing only small scattered areas of sweating.

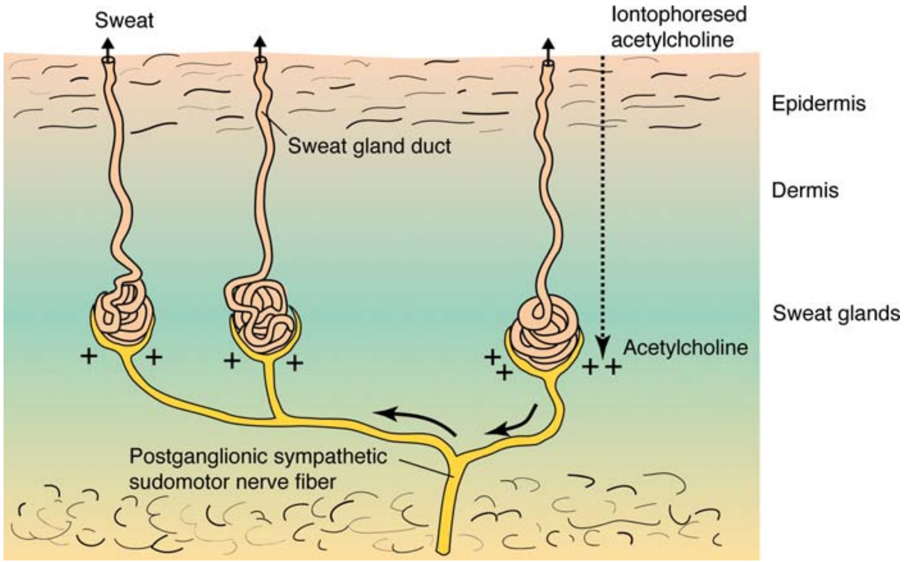
Sweat
Iontophoresed acetylcholine
Epidermis
Sweat gland duct
Dermis
Sweat glands
Acetylcholine
Postganglionic sympathetic sudomotor nerve fiber

FIGURE 8-9 ▪ Sweating induced through an axon reflex. Iontophoresed acetylcholine stimulates sweat gland production locally and—by an axon reflex—in adjacent areas.

there is a reduction in skin resistance. This is the so-called *galvanic skin response*, which can be elicited by painful or emotional stimuli or by deep inspiration.

Sudomotor function has been evaluated also by recording the change in voltage measured from the skin surface after deep inspiration or startle or after electrical stimuli applied to a contralateral mixed or cutaneous nerve at the wrist or ankle (*sympathetic skin response*). Responses are recorded from a pair of electrodes placed on the palm and dorsum of the hand or the sole and dorsum of the foot. The sympathetic skin response is simple to record, but responses tend to habituate and are affected by the recording technique and a number of other factors. The absence of a response, and not the absolute values of latency or amplitude, is regarded as significant for determining abnormality. The normal latency in the upper limb is on the order of 1.5 seconds and in the lower limb is about 2 seconds, reflecting the slow conduction velocity of postganglionic C fibers (approximately 1 m/sec). Abnormalities of the sympathetic skin response reportedly correlate well with the quantitative sudomotor axon reflex test.

Other Studies

PUPILLARY RESPONSES

Pupillary constriction with 2.5 percent methacholine applied locally indicates denervation supersensitivity due to interruption of postganglionic parasympathetic fibers, as in the Holmes–Adie syndrome. Local instillation of 1:1,000 epinephrine hydrochloride (one or two drops) produces little or no response unless there is postganglionic sympathetic denervation, in which case marked pupillary dilatation occurs. A 4 percent solution of cocaine hydrochloride applied to the conjunctival sac dilates the normal pupil, but fails to do so if sympathetic innervation has been interrupted outside the CNS.

RADIOLOGIC STUDIES

Radiologic studies may be helpful in characterizing gastrointestinal and bladder function but are beyond the scope of this chapter.

PATIENT MANAGEMENT

The initial investigative approach to patients presenting with syncope or other symptoms suggestive of postural hypotension or autonomic dysfunction is to exclude reversible causes such as hypovolemia or certain medications, discussed earlier in this chapter. The history must include a detailed account of illnesses and drug intake. An instrument (questionnaire) to assess autonomic symptoms has been developed and validated.[10]

Simple laboratory investigations may include a full blood count and erythrocyte sedimentation rate as well as determination of plasma urea, electrolytes, glucose, morning and evening cortisol levels, and lying and standing catecholamine concentrations.

Urinary screen for porphyrins, serum protein electrophoresis and immunophoresis, hepatic, renal, and thyroid function tests, chest radiograph, and electrocardiogram (to exclude recent cardiac infarction or cardiac ischemia, heart block, or persisting cardiac dysrhythmia) may also be performed, as may serologic tests for syphilis and nerve conduction studies. Neuroimaging studies may be helpful if a structural intracranial lesion is suspected. An echocardiogram may help when evaluating patients with suspected structural lesions of the heart predisposing to syncope. Prolonged tilt-table evaluations and invasive cardiac electrophysiologic studies may be necessary when an arrhythmia is likely. In patients with symptoms of uncertain etiology in whom general medical causes have been excluded, more detailed evaluation of autonomic function in the manner suggested earlier may be helpful.

Treatment

If a specific reversible cause, such as a metabolic or endocrinologic disturbance, can be recognized, it must be treated appropriately. Anemia should be treated. The need for continuing with drugs likely to be responsible should be reviewed and, if feasible, treatment discontinued. Patients should be advised against using alcohol. Treatment with antiarrhythmic agents, cardiac pacemaker, or surgery may be indicated in patients with a cardiac cause of syncope or postural hypotension. Pacemaker therapy may also help patients with syncope due to carotid sinus hypersensitivity. The treatment of POTS was considered earlier.

NONPHARMACOLOGIC MEASURES

If no specific cause can be identified, treatment should be directed to the minimization of symptoms (Tables 8-1 and 8-2). The actual extent to which the blood pressure falls on standing, for example, is of less significance than the occurrence of symptoms. Patients without symptoms generally require no treatment. Symptomatic patients with dysautonomia should avoid extreme heat, alcohol, caffeinated beverages, large meals, rapid postural changes, prolonged periods of recumbency, and excessive straining (e.g., during micturition or defecation), each of which may exacerbate symptoms. Diuretics should be stopped, if possible, and salt intake liberalized.

TABLE 8-1 ■ Management of Postural Hypotension

Treatment of Specific Underlying Cause or Aggravating Factors

- Discontinue drugs that may be responsible, if feasible
- Correct electrolyte/metabolic/hormonal disorders and anemia
- Avoid alcohol and caffeinated beverages
- Eliminate conditions that favor pooling of blood or that impede venous return
- Prescribe antiarrhythmic drugs, pacemaker, or surgery for selected cardiac disorders
- Consider a cardiac pacemaker for carotid sinus hypersensitivity

Symptomatic Treatment

- Nonpharmacologic management
  - Stand up gradually
  - Eat small meals and avoid postprandial activity
  - Wear waist-high elastic stockings
  - Elevate the head of the bed
  - Ingest fluid (approx. 500 ml) before arising
  - Eat a liberal salt diet
- Pharmacologic and other treatment
  - Fludrocortisone
  - Indomethacin; ibuprofen; flurbiprofen
  - Midodrine
  - L-Dihydroxyphenylserine (Droxidopa)
  - Pyridostigmine
  - Sympathomimetic drugs (phenylephrine, ephedrine)
  - Dihydroergotamine; Cafergot
  - Cardiac pacing in selected circumstances
  - Other approaches
    - Vasopressin; desmopressin
    - Erythropoietin
    - Yohimbine
    - Atomoxetine
    - Clonidine
    - Octreotide
    - Norepinephrine (by infusion pump)
    - Deep brain stimulation

When standing, patients often find it helpful to work the leg muscles because this aids the venous return to the heart. Symptoms may also be reduced if patients stand up gradually (e.g., by first adopting the seated position and, after a short pause, getting up from this position). Other physical maneuvers

TABLE 8-2 ■ Mechanisms Involved in the Management of Postural Hypotension by Selected Drugs

Mechanism	Medication
Reduced sodium excretion	Fludrocortisone
Sympathetic vasoconstriction	Midodrine; L-dihydroxyphenylserine; phenylephrine; ephedrine; norepinephrine; yohimbine
β-Blocker with sympathomimetic activity	Pindolol
Enhanced ganglionic cholinergic stimulation (increased total peripheral resistance)	Pyridostigmine
Reduced vasodilatation	Prostaglandin synthetase inhibitors (e.g., indomethacin; ibuprofen; flurbiprofen)
Increased red cell mass	Erythropoietin

that may be helpful include standing with legs crossed, bending forward, squatting, or placing a foot on a chair, thereby slightly increasing the mean arterial pressure so that cerebral blood flow remains adequate. The underlying common mechanism is held to be an increase of thoracic blood volume by transfer from below the diaphragm to the chest. Resistance exercise may increase orthostatic tolerance, plasma volume, and baroreflex gain.

Waist-high elastic stockings may be helpful in alleviating postural symptoms but are often difficult to put on (especially for elderly patients) and may be uncomfortable in hot weather. To be effective, the stockings must extend at least as high as the waist. They should not be worn at night as they may then aggravate nocturnal diuresis. Antigravity suits have been used in the past but are awkward, restrictive, impractical, and not generally available.

Many dysautonomic patients have a disturbance in the regulation of body fluids. In particular, there is defective sodium conservation, especially during recumbency at night, associated with, but not entirely due to, low aldosterone levels; there are also abnormal posture-dependent changes in urine volume (Fig. 8-10), accompanied by an alteration in the secretion of antidiuretic hormone. This leads to relative hypovolemia and postural hypotension that are worse in the morning and improve during the day. The disturbed regulation of body fluids could be due, at least in part, to diminished adrenergic activity in the renal nerves, which affects tubular reabsorption and renin release (and thus angiotensin formation). The effect of recumbency can be minimized by elevating the head of the bed by about 6 inches (20 to 30 degrees), so that the head and trunk are above the legs. This leads to reduced renal artery pressure, thereby stimulating the renin-angiotensin system and promoting sodium retention. Head-up tilt at night reduces nocturnal shifts of interstitial fluid from the legs into the circulation; furthermore, such interstitial fluid may exert hydrostatic force, opposing the tendency of blood to pool in the legs on standing. Head-up tilt at night also reduces supine hypertension.

Patients are sometimes helped by drinking 500 ml water about 15 to 30 minutes before arising from bed in the morning, as this has a transient pressor effect that may diminish postural hypotension at a time when it is usually most troublesome.

PHARMACOLOGIC TREATMENT

If these measures are unsuccessful, the mineralocorticoid fludrocortisone can be tried. This agent seems to exert its effect in part by temporarily increasing plasma volume and also by increasing vascular sensitivity to norepinephrine and improving the vasoconstrictor response to sympathetic stimulation. Treatment is usually commenced with a daily dose of 0.1 mg, which can be increased by 0.1 mg after 2 weeks or so, and then again if necessary. Rare patients may require as much as 0.5 mg daily, but usually a dose of 0.3 mg or less is sufficient. During treatment with fludrocortisone, a positive sodium balance should be ensured, with a sodium intake of at least 150 mEq/day. Side effects include pedal edema, weight gain, recumbent hypertension, cardiomegaly, hypokalemia, and retinopathy; co-existing diabetes mellitus may also be exacerbated.

Prostaglandin synthetase inhibitors should expand plasma volume and inhibit vasodilator prostaglandin synthesis. Indomethacin (25 to 75 mg three times daily with meals) increases peripheral vascular resistance, promotes fluid retention, and may increase the sensitivity of the peripheral vasculature to norepinephrine and angiotensin II. It is said to be helpful in some patients with postural hypotension, especially if they are also on fludrocortisone, but, in general, the results with it have been rather disappointing despite the theoretical advantages of its use. Ibuprofen (200 to 600 mg four times daily before

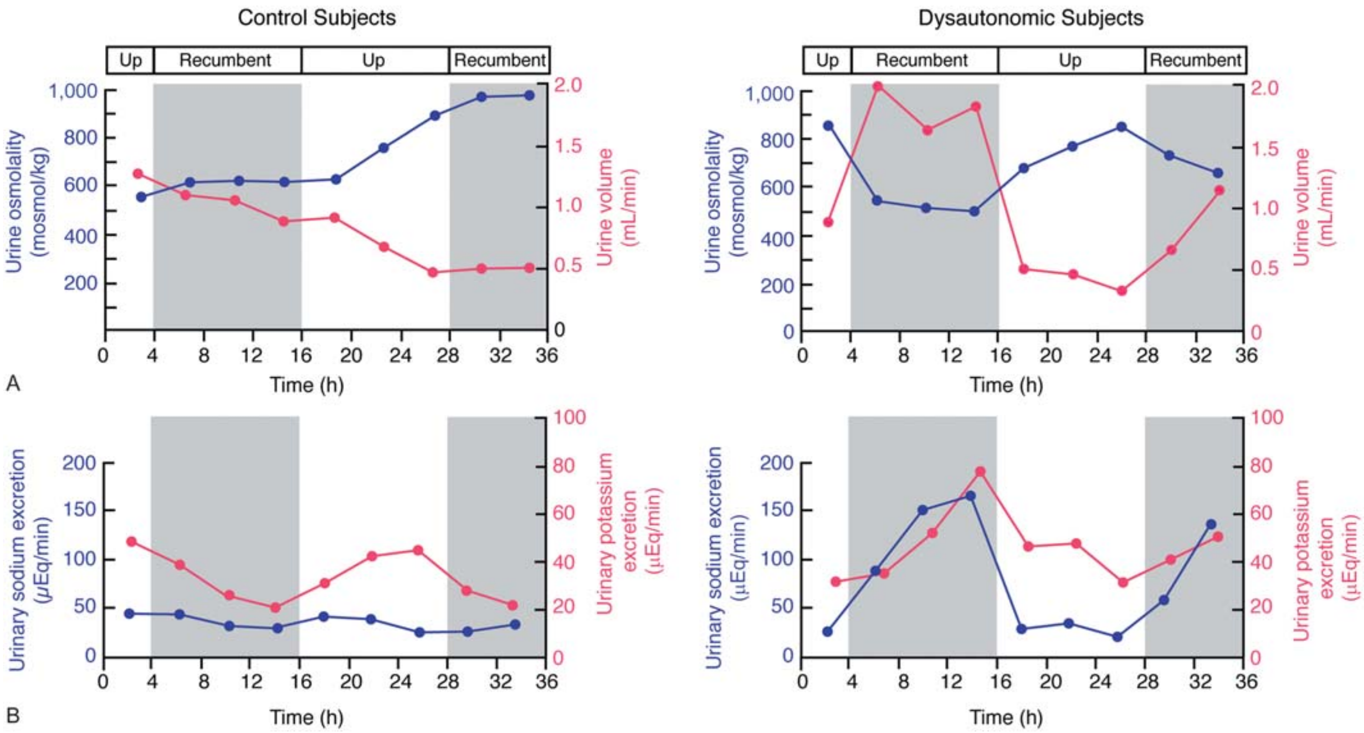

FIGURE 8-10 ■ Renal responses to fluid deprivation for 36 h of five dysautonomic patients with multiple system atrophy (right panels) and four control subjects with Parkinson disease and preserved autonomic reflexes (left panels). Deprivation commenced at 6 P.M. Mean results for each successive 4-hour period are shown for urine osmolality (blue) and volume (red) in *A*, and for sodium (blue) and potassium excretion (red) in *B*. Subjects were recumbent during the night (10 P.M. to 10 A.M.; shaded area) and were up and about during the day (10 A.M. to 10 P.M.). In the control subjects, urine volume declined and osmolality increased during the period of fluid deprivation; sodium excretion was unchanged whereas potassium excretion was greater during the day than night. In the dysautonomic subjects, similar changes were seen during the day; during recumbency at night, however, a considerable increase occurred in urinary volume and sodium and potassium excretion, and urinary osmolality declined. (Data from Wilcox CS, Aminoff MJ, Penn W: Basis of nocturnal polyuria in patients with autonomic failure. J Neurol Neurosurg Psychiatry 37:677, 1974.)

meals) can also be tried and is sometimes helpful. Side effects include gastric irritation, nausea, constipation, and skin rashes. Flurbiprofen has also been used with benefit by some.

Midodrine is a direct α-adrenergic agonist that causes constriction of arterioles and venous vessels. It is started in a low daily dose (2.5 mg three times daily) that is built up gradually to 10 mg three times daily, depending on response and tolerance. Side effects include supine hypertension, piloerection, and pruritus. It is best avoided within 4 hours of bedtime to reduce the risk of nocturnal hypertension.

The use of L-dihydroxyphenylserine (Droxidopa), which is converted by aromatic acid decarboxylase to norepinephrine after oral administration, has been helpful for neurogenic postural hypotension in patients with PAF, Parkinson disease, MSA, dopamine *β*-hydroxylase deficiency, and nondiabetic autonomic neuropathy. Dosage is 100 to 600 mg three times daily, with the last dose taken at least 4 hours before bedtime to reduce the risk of supine hypertension during sleep. The drug is well tolerated, but side effects include headache, nausea, and hypertension.

A related approach is with the off-label use of atomoxetine, which inhibits norepinephrine reuptake. It may helpful for patients with the central lesions of MSA but not for those with a peripheral dysautonomia, in whom any effect on blood pressure is minimal. Its efficacy is currently under study. Side effects include headache, anorexia, nausea, xerostoma, sleep disturbances, depression, behavioral changes, erectile dysfunction, and urinary retention. It may also cause a sinus tachycardia, systolic hypertension, and palpitations.

Pyridostigmine bromide (30 to 120 mg two or three times daily) may reduce postural hypotension by enhancing ganglionic cholinergic transmission without aggravating or precipitating supine hypertension. Its greatest effect is on diastolic blood pressure, suggesting that improvement is due to increased total peripheral resistance. Greater benefit occurs if pyridostigmine is combined with midodrine (5 mg).

There are anecdotal reports of benefit from dihydroergotamine, which is a relatively selective constrictor of peripheral veins. Its action may be mediated partially through α-adrenoreceptors, and enhanced synthesis of a vasoconstrictor prostaglandin may also be important. It is sometimes helpful for treating postural hypotension, but may cause recumbent hypertension. Although it is effective when administered intravenously, its efficacy when taken orally (5 to 10 mg three times daily) is more limited and variable. Inhaled preparations may be effective. Cafergot (caffeine and ergotamine) suppositories have sometimes been helpful.

Sympathomimetic drugs that either act directly to constrict blood vessels (e.g., phenylephrine) or that have an indirect action, preventing the destruction of norepinephrine at sympathetic nerve terminals (e.g., ephedrine, 25 to 50 mg three times daily), have been used to treat postural hypotension. These drugs can sometimes be helpful, but any benefit is often mild and temporary, and they may cause severe recumbent hypertension. Other side effects include nervousness, anxiety, restlessness, tachycardia, and tachyphylaxis.

Octreotide (a somastatin analogue) has also been used, with mixed results and frequent adverse effects, such as nausea, abdominal cramps, flushing, and brady- or tachycardia.

In patients with sympathetic efferent failure, clinical benefit, with a decline in the severity of postural hypotension and an increase in blood pressure on standing, may follow cardiac pacing to protect against vagal overactivity. However, the benefits of this approach are not clear, with benefit reported by some authors but not others in patients with orthostatic hypotension.

Vasopressin responses to upright posture are often defective in autonomic failure, and patients are hypersensitive to exogenous vasopressin. The antidiuretic, V2-receptor specific, vasopressin analogue desmopressin increases the intravascular volume. Intranasal desmopressin administered once at night in patients with multiple system atrophy and nocturnal polyuria has led to an improvement in nocturia without serious adverse effects.[11] If this approach is to be used, serum sodium should be monitored, especially during the first 4 to 5 days of treatment and then at monthly intervals. The long-term therapeutic utility of vasopressin is unclear, however, and treatment with desmopressin should be limited to patients with severe, refractory disease.

Recombinant erythropoietin helps the mild anemia that is common in dysautonomic patients; it increases the red cell mass, blood pressure, and cerebral oxygenation, and reduces postural hypotension.[12] It is expensive, may require concomitant iron supplementation, can lead to thromboembolism or infarction, and sometimes leads to supine hypertension. It can be tried in cases that are otherwise difficult to manage but is otherwise not recommended. It is given subcutaneously, with the dose and frequency of administration individualized.

There have been a variety of other investigative therapeutic approaches. Yohimbine, a centrally acting α_2-adrenoreceptor antagonist, potentiates sympathetic activity and may reduce the postural decline in blood pressure in dysautonomic patients,[13] but its clinical utility and role are not clear because the findings in different studies are inconsistent.[14]

Administration of caffeine with meals may markedly reduce postprandial hypotension and is worthy of trial when symptoms are particularly troubling after meals. A possible role for deep brain stimulation of the periventricular/periaqueductal gray region has been suggested.

Patients with vasovagal syncope require reassurance coupled with advice about ensuring adequate fluid and salt intake and about sympathetic activation techniques (such as isometric hand exercises) to increase the blood pressure[15]; sitting or lying down or sitting with head between the knees may help to abort attacks.

One common consequence of the pharmacologic treatment of postural hypotension is *supine hypertension*. This can be minimized by avoiding lying down during the day, sleeping in the head-up position, and by avoiding pressor agents within 3 hours of bedtime. A carbohydrate snack at bedtime may also help, but fluid intake should be limited. Monitoring the nocturnal blood pressure also provides useful information about the severity of hypertension and whether it persists throughout recumbency. If supine hypertension persists, pharmacologic treatment may be necessary but risks worsening postural hypotension.[16]

The effects of impaired thermoregulatory sweating may be alleviated by external temperature regulation, such as by air conditioning. High-fiber diets, bulking agents, fecal softeners, laxatives, osmotic agents (e.g., lactulose), and glycerine suppositories may reduce constipation. Depending on their nature, urinary disturbances may be helped by bladder training and timed urination, avoidance of diuretics and certain foods and beverages, physical therapy to strengthen the pelvic floor muscles, anticholinergic medications, intermittent self-catheterization or suprapubic catheterization, and measures to contain incontinence such as penile sheaths and pads. The treatment of erectile dysfunction is discussed in Chapter 30.

General Precautions in Dysautonomic Patients

Patients may show postprandial falls in blood pressure because blood is diverted to the hepatic and splanchnic beds. Vasoactive substances may also contribute to the hypotensive response. To avoid or minimize this postprandial hypotension, it is helpful to eat smaller meals and to avoid excessive activity during the immediate postprandial period.

Dysautonomic patients often have low circulating catecholamine levels and denervation supersensitivity to sympathomimetic amines. Medications containing such substances should therefore be avoided, even though they are often available without prescription in over-the-counter preparations.

Patients with dysautonomia pose special problems during anesthesia. They are unable to tolerate hemodynamic stresses normally because of impaired cardiovascular reflexes. Maintenance of fluid balance is more difficult because of the abnormal manner in which they handle salt and water, and their enhanced sensitivity to volume changes influences blood pressure control.

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CHAPTER

9

Neurologic Complications of Cardiac Arrest

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HYPOXIC-ISCHEMIC ENCEPHALOPATHY
TARGETED TEMPERATURE MANAGEMENT
PROGNOSTIC DETERMINATION
  Prognostication in the Absence of Targeted Temperature Management
  Targeted Temperature Management and the Neurologic Examination
  Specifics of the Cardiac Arrest
  Electrophysiologic Tests
  Neuroimaging
  Biomarkers
  Multimodal Prognostication Algorithms
ETHICAL CONSIDERATIONS
  Accurate Prognostication
  Discussion with Surrogate Decision-Makers

Despite advances in the management of cardiac arrest, patients continue to have high mortality, exceeding 90 percent. Following the return of spontaneous circulation, dysfunction of multiple organ systems along with a systemic inflammatory response, collectively termed the "post-arrest syndrome," can lead to substantial morbidity. The diagnosis of primary hypoxic-ischemic brain injury and the prevention of secondary neurologic injury are the primary goals of early management. Persistence of coma or the prediction of long-term severe neurologic deficits commonly leads to withdrawal of life support; therefore, accurate prediction of neurologic outcome early after resuscitation is important. This chapter reviews the pathophysiology of hypoxic-ischemic brain injury and the neuroprotective mechanisms of therapeutic hypothermia (TH). In addition, the clinical, biochemical, radiographic, and electrophysiologic tests used to predict neurologic outcome following cardiac arrest are reviewed, as are the ethical implications that follow prognostication.

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

There is a delay between the time of ischemic cell injury and the manifestation of cell death. This delay may be hours or up to 4 days following the initial insult. During cardiac arrest, oxygen levels decline, cerebral blood flow ceases, and cells must switch to anaerobic metabolism in order to produce adenosine triphosphate (ATP). Anaerobic glycolysis leads to an accumulation of hydrogen ions, phosphate, and lactate, all of which result in intracellular acidosis. The resulting excess of hydrogen ions displaces calcium from intracellular proteins, increasing its intracellular concentration. Dysfunction of the Na^+/K^+ ATP pump and ATP-dependent channels leads to further increases in intracellular calcium. In addition, hypoxia results in the release of excitatory neurotransmitters, such as glutamate, that cause the endoplasmic reticulum to release calcium stores. This excess calcium activates intracellular proteases and leads to further release of excitatory neurotransmitters following

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depolarization of the cell membrane. Activation of *N*-methyl-D-aspartate (NMDA) glutamate receptors results in sodium and chloride influx, leading to hyperosmolarity that causes water influx and neuronal death.[1] Restoration of the circulation can lead to further glutamate release and the formation of oxygen-derived free radicals and reperfusion injury, which can cause additional damage.[1] In addition, apoptosis, due to caspase-3 activation in neurons and oligodendroglia in the cerebral neocortex, hippocampus, and striatum, can contribute to cell death, at least in perinatal models of anoxia-ischemia.[1]

Distinct brain regions and specific neuronal populations appear more susceptible to hypoxic-ischemic injury, probably due to their location in a vascular border-zone or to higher metabolic rates requiring increased oxygen or density of various glutamate receptors on neuronal membranes.[1] The CA1 neurons of the hippocampus are the most sensitive to ischemia, and injury commonly results in memory dysfunction. The Purkinje cells of the cerebellum, the pyramidal neurons in layers 3, 5, and 6 of the neocortex, and the reticular neurons of the thalamus are also commonly affected. In addition, three vascular border-zones are susceptible to a reduction in blood flow due to their distance from the parent vessel; these areas become clinically important in cases of severe hypotension and incomplete cardiopulmonary arrest. The cortical border-zones are the anterior border-zone between the anterior cerebral artery and the middle cerebral artery territories and the posterior border-zone between the middle cerebral artery and posterior cerebral artery territories. Infarction of the anterior border-zone results in brachial diplegia, or "man-in-a-barrel" syndrome. Infarction of the posterior border-zone results in visual deficits including cortical blindness if bilateral. The internal, or subcortical, border-zone is found at the junctions between the branches of the anterior, middle, and posterior cerebral arteries with the deep perforating vessels, including the lenticulostriate and anterior choroidal arteries.

TARGETED TEMPERATURE MANAGEMENT

The use of TH in patients after cardiac arrest was first reported in the 1950s, but the complication rate was high and results were inconclusive. In 2002, two landmark studies were published showing that TH improves neurologic outcomes following cardiac arrest when the initial rhythm was ventricular fibrillation (or possibly pulseless ventricular tachycardia). Patients randomized to moderate hypothermia (32° to 34°C) had a more favorable neurologic outcome, defined as Cerebral Performance Category (CPC) 1 (normal) or 2 (moderate disability), compared with controls randomized to standard care. No significant differences were found between the groups with respect to complications, including bleeding, infection, and arrhythmias, and the number needed to treat in these trials was impressively in the single digits.[2]

However, whether the therapeutic benefit observed in these trials was due to TH or fever prevention remained unclear until publication of the targeted temperature management (TTM) trial in 2013. This study randomized patients to moderate hypothermia (32° to 34°C) or 36°C for 24 hours, followed by 48 hours of fever prevention using acetaminophen and surface cooling in both groups. No difference was observed in outcome, with 46 to 48 percent of patients in both groups achieving a CPC of 1 or 2 at 6 months, a rate similar to that observed in the treatment arms of both 2002 TH studies.[2] This study is the basis for current guidelines that recommend a target temperature of 32° to 36°C for 24 hours, followed by 48 hours of fever prevention.[2]

There are many postulated mechanisms to explain the neurologic benefits that occur with TH, including a decrease of the extracellular levels of excitatory neurotransmitters such as glutamate and dopamine. The NMDA receptor is glycine dependent, and TH has been shown to decrease cerebral levels of glycine following ischemia, and thus to lessen glutamate-related hyperexcitability. TH reduces the proliferation of astroglial cells and their release of inflammatory cytokines and free radicals. TH also results in decreased cerebral blood flow as well as decreased metabolism and oxygen and glucose utilization. Conversely, fever may exacerbate brain injury following cardiac arrest due to increased glutamate production and excitotoxicity, increased cerebral metabolism, blood–brain barrier permeability leading to hyperemia, cerebral edema, and increased intracranial pressure.[1]

PROGNOSTIC DETERMINATION

Following return of spontaneous circulation, neurologists are often consulted to determine prognosis, specifically the probability of regaining consciousness and of the likely presence, severity, and extent of any persistent neurologic deficits. While prognostication with 100 percent certainty is not possible, a reasonable goal is to identify those patients who will have severe neurologic deficits with complete dependency at 6 months. Because many patients and their families choose withdrawal of life support when faced with this unfavorable prognosis, it is essential that the combination of clinical, radiographic, and electrophysiologic tests used to arrive at this conclusion therefore have a positive predictive value (PPV) as close to 100 percent as possible.

Much of the published literature attempts to predict which patients will have a CPC of 3 or greater 6 months after cardiac arrest.[3] Such an outcome includes death, vegetative state, and severe disability with dependency on caregivers for daily support. However, because studies of prognosis after cardiac arrest include patients whose families elected to withdraw life support, the true range of long-term functional outcomes remains unknown and the prognostication algorithms discussed in this chapter suffer from the risk of self-fulfilling prophecy. In addition, because studies tend to group CPC 3 to 5 and label them all "unfavorable," distinguishing between the possibility of severe disability with dependency but some retained ability to communicate or even ambulate (CPC 3) and a persistent vegetative state or death (CPC 4 or 5) remains difficult.[3] Further complicating prognosis and blurring the lines of what some consider meaningful recovery is the discovery through functional brain imaging techniques that some patients in a persistent vegetative state retain awareness and potentially even comprehension of spoken language.

Most studies of prognosis after cardiac arrest report false-positive rates (FPRs), yet this is a difficult number to translate for families. In prognostic studies, true positives are generally defined as patients with a poor prognostic sign who have a poor outcome, and false positives are those with a poor prognostic sign who have a good outcome. The FPR (or 1-specificity) is determined by dividing the number of false positives by the number of patients who had a good outcome. In lay terms this can be stated as the percentage of patients with good outcome who had the poor prognostic sign, a number that carries little practical meaning. The PPV provides more clinically relevant information: the percentage of patients with a poor prognostic sign who have a poor outcome. Surrogate decision-makers want to know (1−PPV), or the chance that a patient with the poor prognostic sign will still have a good outcome. When there are more patients with a good outcome than patients with a specific poor prognostic sign, (1−PPV) is often larger than the FPR, and thus the FPR can be misleadingly low.

No neurologic prognostication should occur until a minimum of 24 hours after the arrest; in patients treated with TTM, it may take days to establish a prognosis because both the lowered temperature and associated sedation required may profoundly affect clinical and electrophysiologic findings. The neurologic examination should be performed approximately 72 hours after the arrest and all sedatives should be discontinued with enough time for them to have reliably cleared from the body. The examination should focus on the level of consciousness, the pupillary light reflex, corneal reflex, spontaneous eye movements, the oculocephalic reflex, and the motor response to central and peripheral painful stimuli. Quantitative pupillometry is less likely to mistake minimally reactive pupils for unreactive pupils and is therefore preferred to the standard pupillary light reflex.[4] The presence of status myoclonus, defined as spontaneous, repetitive, unrelenting, and generalized myoclonus affecting the face, limbs, and axial musculature lasting more than 30 minutes should be noted. Electroencephalography and somatosensory evoked potentials (SSEPs) are performed after rewarming, between 24 and 72 hours after the arrest, and serum neuron-specific enolase can be measured at 24, 48, and 72 hours. The combination of clinical, electrophysiologic, and serum biomarker data derived from these tests forms the basis of the modern multimodal approach to prognostication.[2]

Prognostication in the Absence of Targeted Temperature Management

Prognostication following cardiac arrest is largely based on the work of Levy and colleagues, who analyzed a single cohort of 210 patients and identified factors that could accurately predict, at various time points post-arrest, a poor neurologic outcome.[4] In 2006, the American Academy of Neurology (AAN) published practice parameters that summarized the available literature and provided an algorithm to establish prognosis.[4] In patients who remain comatose but do not meet criteria for brain death, clinical signs and electrophysiologic tests can be used to establish a poor prognosis. The clinical signs that predicted poor neurologic outcome were status myoclonus on day 1 (FPR 0%, CI 0−8.8), absence of the pupillary light reflex or corneal reflex on day

3 (FPR 0%, CI 0–3), and best motor response of extension or worse on day 3 (FPR 0%, CI 0–3). SSEPs recorded between days 1 and 3 demonstrating bilaterally absent N20 responses also predicted poor outcome (FPR of 0.7%, CI 0–3.7). Serum neuron-specific enolase (NSE) levels greater than 33 μg/L on days 1 to 3 were also a negative prognosticator (FPR 0%, CI 0–3).[4] These practice parameters allow a physician to identify patients who will almost certainly have a poor neurologic outcome, but it is important to note that many other patients not meeting these criteria will also have a poor outcome.

Caution must be exercised when applying these prognostic criteria to patients who have undergone TTM, a well-established confounder of the neurologic and electrophysiologic examination, as the practice parameters were based on literature published before its widespread adoption.

Targeted Temperature Management and the Neurologic Examination

Soon after the introduction of TH, some clinical signs including the pupillary light reflexes, corneal reflexes, motor responses, and presence of status myoclonus were found to have reduced accuracy for predicting poor neurologic outcome. Among patients treated with TTM, no features of the neurologic examination at 24 hours after the arrest reliably predict outcome, and determination of brain death should wait until it is certain that the effect of sedation and hypothermia are negligible. At 72 hours after the arrest, the absence of pupillary light reflexes and the absence of corneal reflexes have a reasonably high PPV for a poor outcome, but rare patients with these findings will recover with good outcome (Table 9.1). Patients with extensor posturing or no motor response at 72 hours recover functional independence at a high enough rate that this sign is no longer considered a reliable prognostic indicator. Conversely, patients with flexor or better motor response at 72 hours have a 67 percent chance of recovering the ability to function independently (Table 9.2).

Myoclonus may arise from the cerebral cortex, subcortical structures such as the thalamus, or brainstem. The cortical form, unlike the brainstem form, has a reliable correlate on the electroencephalogram (EEG). The presence of status myoclonus was considered uniformly fatal based on studies in the prehypothermia era; postmortem studies found severe damage to various gray matter structures in the brain

TABLE 9-1 ■ Poor Prognostic Signs and Their Test Characteristics

Prognostic Sign	Patients with Sign		Patients without Sign		PPV (95% CI)	FPR (95% CI)
	Poor Outcome	Good Outcome	Poor Outcome	Good Outcome		
Absent bilateral pupillary light reflex[7,11–15]	161	5	124	177	97% (94–100)	1.4% (0.2–2.7)
Absent bilateral corneal reflex[7,11–15]	213	10	104	175	96% (93–98)	3.2% (1.2–5.1)
No or extensor motor response to pain[7,11–17]	623	69	203	417	90% (88–92)	14% (11–17)
Status myoclonus[7,13,17,18]	178	6	639	671	97% (94–99)	0.9% (0.2–1.6)
Absent bilateral median SSEP [7,12–17]	265	1	316	219	99.6% (99–100)	0.5% (0–1.3)
Highly malignant EEG (suppressed background with or without continuous periodic discharges, burst suppression)[5,6,15,19,20]	208	1	259	225	99.5% (99–100)	0.4% (0–1.3)

PPV, positive predictive value (likelihood of poor outcome in patients with poor prognostic sign); FPR, false-positive rate; CI, confidence interval; SSEP, somatosensory evoked potential; EEG, electroencephalogram. Results are pooled from multiple studies that assessed outcome at 3 or 6 months. Neurologic examination performed off sedation and after rewarming. Status myoclonus defined as spontaneous, repetitive, unrelenting, and generalized myoclonus affecting the face, limbs, and axial musculature lasting more than 30 minutes. SSEP performed after rewarming. Some studies define burst suppression by >10 percent background suppression, others by >50 percent.

TABLE 9-2 ■ Favorable Prognostic Signs and Their Test Characteristics

Prognostic Sign	Patients with Sign		Patients without Sign		PPV (95% CI)
	Good Outcome	Poor Outcome	Good Outcome	Poor Outcome	
Flexor or better motor response to pain[7,11–17]	417	203	69	623	67% (64–71)
Benign EEG (reactive, continuous background, or no malignant features)[5–7,15,17,20]	335	171	46	433	66% (61–70)

PPV, positive predictive value (likelihood of good outcome in patients with good prognostic sign); CI, confidence interval; EEG, electroencephalogram. Results are pooled from multiple studies that assessed outcome at 3 or 6 months.

and spinal cord in these patients, demonstrating the cause of death to be hypoxic-ischemic insult rather than status epilepticus. However, cases of good outcome despite status myoclonus in patients treated with TTM indicate the presence of this sign is suggestive of a poor neurologic outcome but should not be used in isolation to prognosticate (Table 9.1).[4]

Following cardiac arrest, many patients have confounders of the neurologic examination other than hypothermia, including cardiogenic shock, metabolic acidosis, and other metabolic derangements that must be accounted for when interpreting the examination. Organ failure, especially hepatic and renal dysfunction, may cause reversible encephalopathy and cloud the predictive power of the neurologic examination. Comatose patients require sedation for presumed pain or distress, ventilator asynchrony, or as part of many TTM protocols; clearance of these drugs may be delayed due to organ dysfunction. TTM itself can also result in increased serum concentrations of certain drugs, increased duration of action, and decreased clearance, including fentanyl, midazolam, propofol, and neuromuscular blocking agents. These drugs are commonly used in TTM protocols, rendering the neurologic examination unreliable for prognostication until they are sufficiently cleared.

Specifics of the Cardiac Arrest

Characteristics of the cardiac arrest, including anoxia time (the time from onset to initiation of cardiopulmonary resuscitation) and total arrest duration, have been explored as predictors of prognosis. Although longer anoxia time and duration of resuscitation are associated with poorer outcomes, these associations are not specific enough to be useful for prognostication purposes.[2] Prognosis is more favorable after arrest due to shockable (ventricular fibrillation or pulseless ventricular tachycardia) than nonshockable rhythms (asystole or pulseless electrical activity), but similarly, there are enough survivors with good outcome after the latter to preclude the use of initial rhythm for prognostication.

Electrophysiologic Tests

Electrophysiologic tests, including SSEPs and EEG, can aid in prognostication after cardiac arrest. The most common SSEP utilized involves stimulation of the median nerve at the wrist and recording the response over the contralateral scalp, specifically over the primary somatosensory cortex. In a normal adult, this response occurs 20 msec from the time of median nerve stimulation and is therefore called the N20 response (Fig. 9-1). During this test, additional electrodes are placed over Erb's point (over the brachial plexus) and high on the posterior neck (over the dorsal columns of the spinal cord); stimulation of the median nerve results in responses at these electrodes at approximately 9 and 13 msec, respectively. These N9 and N13 responses, along with the N20, examine the continuity of the nervous system from the median nerve through the brachial plexus and high cervical cord to the cortex and reduce false-positive results from conduction problems below the cranium. Among patients treated with TTM, the vast majority with bilaterally absent N20 responses have poor neurologic outcomes (Table 9.1). Very rare patients have

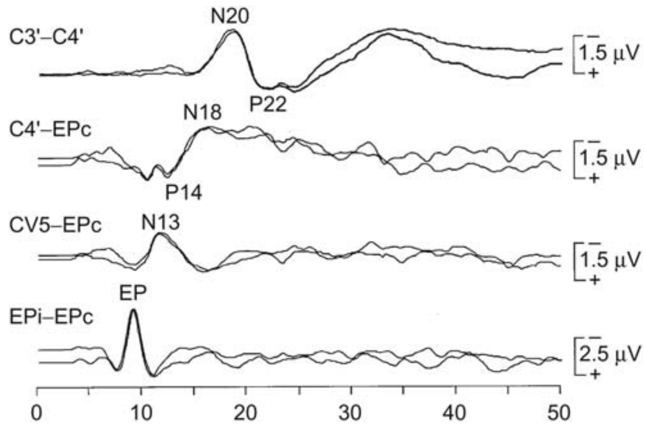

FIGURE 9-1 ▪ Normal somatosensory evoked potential elicited by stimulation of the right median nerve at the wrist. Responses were recorded over the brachial plexus at ipsilateral Erb point (EPi), over the fifth cervical spine (CV5), and over the ipsilateral scalp (C4′) with the contralateral Erb point (EPc) used as a reference, as well as over the contralateral scalp (C3′) referenced to the ipsilateral scalp (C4′). An N9 potential is seen over the Erb point, an N13 over the cervical spine, subcortical far-field P14 and N18 potentials over the ipsilateral scalp area, and an N20 over the contralateral "hand" area (C3′) of the scalp. Loss of the N20 response bilaterally (with preserved N9 and N13 responses) portends a poor neurologic prognosis. (From Aminoff MJ, Eisen A: Somatosensory evoked potentials. p. 581. In Aminoff MJ (ed): Aminoff's Electrodiagnosis in Clinical Neurology. 6th Ed. Elsevier, Oxford, 2012, with permission.)

survived with good outcome, again emphasizing that in patients who have undergone TH, no test should be used in isolation to determine prognosis.

The EEG may be used to prognosticate after cardiac arrest when interpreted using a set of standard criteria. Westhall and colleagues recorded routine EEGs 12 to 36 hours after rewarming in patients who remained comatose in the TTM trial and categorized the EEG patterns as highly malignant, malignant, or benign based on American Clinical Neurophysiology Society terminology.[5] Highly malignant EEG patterns included a suppressed background without discharges; a suppressed background with continuous periodic discharges; or a burst-suppressed background with or without periodic discharges (with suppression $<10\ \mu\text{V}$ constituting $>50\%$ of the recording, Fig. 9-2). Malignant EEGs demonstrated malignant periodic or rhythmic patterns (abundant periodic discharges, abundant rhythmic polyspike-/spike-/sharp-and-wave, unequivocal electrographic seizure); malignant background (discontinuous background, low-voltage background, reversed anterior–posterior gradient); or unreactive EEG (absence of background reactivity or only stimulus-induced discharges). Benign EEGs were defined as those without any malignant features (but not necessarily reactive).

The prognostic value of EEG was first reported in 103 patients at 8 centers in the TTM trial, and later in 207 patients at 20 additional centers. A highly malignant EEG pattern had a PPV for CPC 3 to 5 of 98.8 percent (CI 96.4–100).[6] The single false-positive patient was sedated during the EEG, emphasizing the need to consider the role of sedation in EEG interpretation. Several other studies have reported similar findings (Table 9.1). EEG reactivity is defined as a change in frequency or amplitude that occurs in response to verbal or noxious stimuli and is a marker of good prognosis following cardiac arrest. In a study of 357 patients who underwent EEG after cardiac arrest at two large medical centers, both early (during TTM) and late (after return to normothermia and off sedation) reactive EEG was predictive of eventual CPC 1–2 with a PPV of 72 and 69 percent, respectively (Table 9.2).[7]

After cardiac arrest, up to one-third of patients may develop electrographic status epilepticus.[4] Electrographic status epilepticus is most often associated with clinical myoclonus, but may also be subclinical or associated with generalized tonic-clonic convulsions. Post-hypoxic status epilepticus is a poor prognostic sign, but enough patients survive with good functional outcome that seizures should be treated aggressively unless other prognostic criteria indicate a poor prognosis.

The EEG may also help identify patients with a favorable prognosis among those with status myoclonus. Most patients with status myoclonus will have a highly malignant EEG with a burst-suppressed background; outcome in such patients is very poor.[8] Rare patients with status myoclonus demonstrate a more benign EEG pattern, with a continuous background and epileptiform discharges correlating only to myoclonic jerks; four of eight such patients (from a total of 69 patients with status myoclonus) awoke and survived to discharge home or to rehabilitation in one study.[8]

Neuroimaging

Computerized tomographic (CT) imaging performed early after cardiac arrest is usually normal, although in severe cases of hypoxic-ischemic injury,

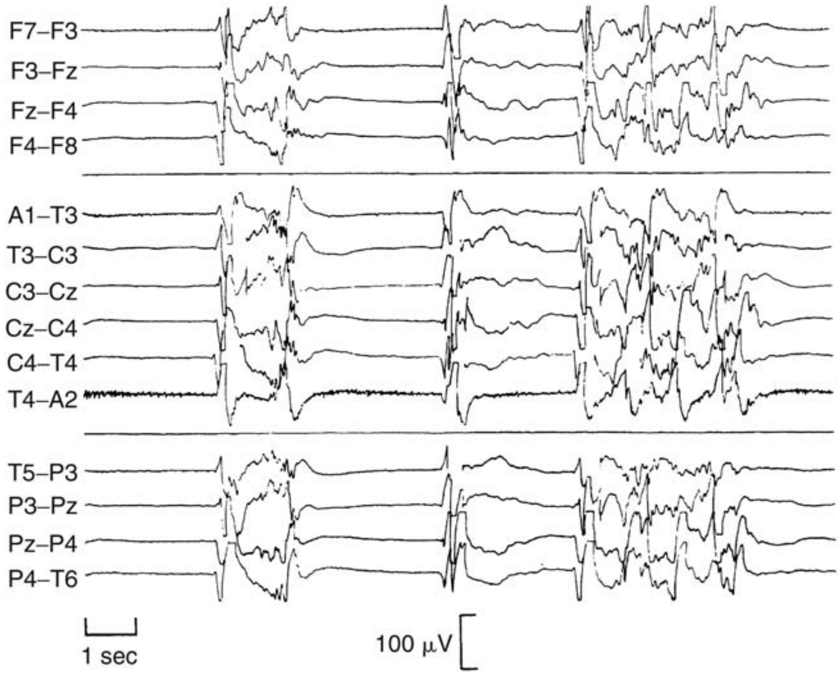

FIGURE 9-2 ■ Burst-suppression pattern recorded in the EEG of a 70-year-old man after a cardiac arrest from which he was resuscitated. (From Aminoff MJ: Electroencephalography: General principles and clinical applications. p. 37. In Aminoff MJ (ed): Aminoff's Electrodiagnosis in Clinical Neurology. 6th Ed. Elsevier, Oxford, 2012, with permission.)

loss of gray–white differentiation and cerebral edema may be seen. Out-of-hospital cardiac arrest has been associated with both subarachnoid and intraparenchymal hemorrhage in as many as 10 percent of patients, and therefore routine brain CT is recommended in European resuscitation guidelines to rule out these possibilities. Both CT and magnetic resonance imaging (MRI) have been studied as a prognostic tool.[4] Several retrospective studies identified decreased gray–white attenuation ratios on CT as a marker of poor prognosis. Abnormal diffusion-weighted imaging and the related apparent diffusion coefficient (ADC) on MRI correlates with poor neurologic outcomes. Attempts have been made to establish cut-points for total area of reduced ADC that has a high PPV for poor outcome, but further validation is needed. Other brain MRI modalities such as diffusion tensor imaging and functional MRI are also being investigated as prognostic tools.

Biomarkers

Several biomarkers have demonstrated potential for prognostication following cardiac arrest. The use of serum or cerebrospinal fluid (CSF) biomarkers is appealing as it does not require either patient transport or trained technicians, nor are the levels affected by sedation. NSE is a gamma isomer of enolase, an intracytoplasmic enzyme found in neurons and neuroectodermal cells. Damage to neurons results in release of NSE into the CSF and eventually it is measurable in the serum. The threshold of NSE above which a poor prognosis can be predicted with an acceptably low FPR varies depending on the laboratory performing the test, the timing between the arrest and blood sampling, and whether or not the patient was treated with TTM. A meta-analysis of multiple studies in patients treated with TTM found thresholds associated with a 0 percent FPR of 49.6 to 151.4 μg/L at 24 hours; 25 to 151.5 μg/L at 48 hours; and 57.2 to 78.9 μg/L at 72 hours.[2] In the TTM trial, thresholds with 0 percent FPRs were 107, 120, and 50 μg/L at 24, 48, and 72 hours, respectively.[4] While no universally accepted value of NSE definitively predicts poor outcome, using the upper limit of these ranges is a reasonable approach.

S100B is a calcium-binding protein secreted by glial and Schwann cells. It may also act as a cytokine, resulting in neuronal apoptosis, and it has a biologic half-life of 2 hours. When it is elevated in the serum after cardiac arrest, neurologic outcome is generally poor, but measuring S100B does not appear to add prognostic information to NSE. More promising is serum neurofilament light chain (NFL), a neuronal cytoplasmic protein expressed in myelinated axons and released into the CSF and blood after neuronal injury. After cardiac arrest, there appears to be less overlap between values in patients with good and poor prognoses, but this finding needs to be validated in prospective studies. In addition, serum NFL may be elevated in a wide range of neurologic disorders, and it is not known how it may inform prognosis in patients with pre-existing neurologic conditions.

Multimodal Prognostication Algorithms

Ensuring the presence of at least two negative prognosticators can improve prognostic accuracy. Among 134 patients treated with TH at 33°C, two or more of the following negative prognostic findings demonstrated a PPV of 100% for CPC 3 to 5: at least one absent brainstem reflex (pupillary, corneal, or oculocephalic) at 72 hours, myoclonus, unreactive EEG during TH and after rewarming, and bilaterally absent N20 responses in the median-derived SSEP performed after rewarming.[9] A second study of 61 patients treated at 36°C found 100% PPV for CPC 3 to 5 with the presence of two or more of the following negative prognostic findings: unreactive first EEG (performed at least 6 hours after arrest but during TTM and under sedation); epileptiform findings on the first EEG; absent pupillary reflex, corneal reflex, or both at 72 hours; early myoclonus; bilaterally absent SSEP measured at least 24 hours after arrest; and NSE $>75\ \mu g/L$ (the higher value of measurements taken at 24 and 48 hours).[10]

Most of the literature on prognosis following cardiac arrest aims to identify with accuracy those patients who will die or be left severely disabled with complete dependency. However, many patients who do not have these prognostic signs will also have a poor outcome. For example, the negative predictive values of the two prognostic algorithms described above are approximately 60 percent, meaning that 40 percent of the patients without two negative prognostic signs will also have a poor outcome. Further research is needed to help differentiate those patients who will have near-complete neurologic recovery from those who will have moderate disability.

ETHICAL CONSIDERATIONS

Patients who have been resuscitated from cardiac arrest and are left with significant neurologic deficits pose several ethical challenges. Physicians tend to overestimate poor outcomes and underestimate good outcomes, especially in the first days following arrest. Some families express doubt about the accuracy and sincerity of physicians' prognostic opinions and management suggestions. Ultimately, however, what experts say to families, fellow physicians, and other caregivers has enormous influence. There is a need for accuracy, honesty, frankness, consideration, acknowledgment, and patience in discussions that involve possible end-of-life decisions. The principal issues include accurate prognostication and discussions with surrogate decision-makers, in which the autonomy of the patient is given primacy.

Accurate Prognostication

Most of this chapter has been devoted to accurate prognostication. Using the results of studies, it should be possible in most patients to arrive at some estimate of the probability that recovery of awareness will occur. In some cases, the prognosis will remain uncertain and more time and possibly more or repeated testing will be necessary.

Discussion with Surrogate Decision-Makers

Patient autonomy is given the greatest priority in most North American and European cultures. After cardiac arrest, patients generally are unable to participate in discussions regarding prognosis and management, and so this responsibility falls to surrogate decision-makers. In hierarchical order, this person is typically: the spouse or partner, children older than 18 years, a parent or guardian, a sibling, or the closest next-of-kin. In some cases, the surrogate decision-maker is identified in a Power of Attorney statement or similar document. In rare cases, no person can be identified and a public trustee is often then appointed.

Research indicates that there are often problems in the communication between physicians and surrogate decision-makers in the critical care setting. Often surrogate decision-makers experience anxiety and depression, and these issues can interfere with comprehension and executive decision-making functions. Physicians, along with nursing staff, need to be sensitive to these issues and involve surrogate decision-makers in repeated discussions while providing empathy and support. Information pamphlets or visual aids may be helpful in improving comprehension of the severity of the illness. If the neurologist will be involved in discussions of prognosis and goals of care with the family, it is helpful to meet the family on the first hospital day to establish rapport and orient the surrogate decision-maker to the neurologist's role, even though no prognostic information can be given at this early stage.

A good starting point for discussion is to ask surrogate decision-makers about their understanding of the patient's illness—further explanation and clarification then follow. Surrogate decision-makers should be forewarned if there is "bad news," and the emotional reaction acknowledged. They need to understand that they are speaking for the patient and should be encouraged to help the healthcare team understand what the patient would want to do, given the prognosis provided. Surrogate decision-makers should be asked whether there are advance directives, either written or verbally stated, which may give a clear idea of the patient's perspectives, at least at some point in the past. If there are no clear advance directives, surrogate decision-makers and family members are asked to describe their understanding of the patient's values and to formulate a response for him or her.

Occasionally differences of opinion among family members arise or the surrogate decision-maker cannot make a decision. Cultures also vary in their view of what constitutes meaningful recovery, and even if the medical team is convinced that the patient will not recover beyond a vegetative state, this may be acceptable to some families. Physicians should maintain respect and understanding, while providing further meetings. Involvement of an ethicist or a member of the clergy is sometimes helpful. In rare instances the issue needs to be resolved legally, either in court or by the appointment of a special board.

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CHAPTER

10

Cardiac Manifestations of Acute Neurologic Lesions

CHUNG-HUAN SUN ■ NERISSA U. KO

HISTORICAL PERSPECTIVE

ANATOMY AND PHYSIOLOGY
- Medullary Control of Cardiovascular Function
- Paraventricular Nucleus of the Hypothalamus
- The Limbic System and Amygdala
- Insular Cortex

MECHANISM OF NEUROCARDIOGENIC INJURY
- Catecholamine Surge on Cardiomyocytes
- Catecholamine Surge on Coronary Microvasculature

CARDIAC MANIFESTATIONS OF GLOBAL NEUROLOGIC INJURY
- Reduced Left Ventricular Function
- Regional Wall Motion Abnormalities
- Cardiac Biomarkers of Neurologic Injury
  - *Creatine Kinase-MB*
  - *Troponin*
  - *B-Type Natriuretic Peptide*

CARDIAC MANIFESTATIONS OF FOCAL NEUROLOGIC INJURY
- Electrocardiographic Findings
  - *QT Prolongation*
  - *Repolarization Abnormalities*
  - *Q Waves and U Waves*
- Disturbances of Cardiac Rhythm
  - *Arrhythmias*
  - *Heart Rate Variability and Baroreceptor Reflex Sensitivity*

EPILEPSY AND TRAUMA
- Epilepsy
- Traumatic Brain Injury

CARDIAC EVALUATION

CLINICAL MANAGEMENT

CONCLUDING COMMENTS

Cardiac abnormalities are common after acute neurologic injury. Disturbances can range in severity from transient electrocardiographic (ECG) abnormalities to profound myocardial injury and dysfunction. Evidence from animal models and clinical observations indicate that the central nervous system (CNS) is involved in the generation of cardiac arrhythmias and dysfunction even in an otherwise normal myocardium. Neurologic lesions may influence cardiovascular function and affect cardiac prognosis, and—in addition—the presence of cardiac abnormalities may be associated with poor neurologic outcomes. A better understanding of cardiac abnormalities after acute neurologic injury can improve the clinical management of patients and may also have important prognostic implications.

This chapter briefly outlines the cardiac manifestations that follow acute neurologic injury, summarizes the neurophysiology and neuroanatomy of cardiac control, and discusses the clinical implications and diagnostic and treatment recommendations for the most common cardiac complications.

HISTORICAL PERSPECTIVE

Harvey Cushing first described hemodynamic changes after acute intracerebral hemorrhage (ICH) in 1903. The bradycardia and hypertension in response to increased intracranial pressure (ICP), known as the Cushing reflex, was later proved in animal models to be mediated by the CNS. Over subsequent decades, clinical observations began to identify the importance of the brain–heart interaction in patients with cerebral lesions. Cardiac abnormalities were described with various CNS diseases including seizures, trauma, ischemic stroke, and ICH, and less commonly with tumors, electroconvulsive therapy, and meningitis.

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Cardiac pathology with features of subendocardial hemorrhage was observed in neurologic patients without known previous cardiac disease. After World War II, patients with subarachnoid hemorrhage (SAH) were noted to have cardiac myocytolysis similar to that in pheochromocytoma. An emotional- and stress-induced cardiomyopathy was then described in Japan, and subsequently reported in other populations.

ANATOMY AND PHYSIOLOGY

Medullary Control of Cardiovascular Function

The interplay between the heart and brain is best exemplified through the medullary control of the autonomic nervous system. Disruptions to this pathway can lead to arrhythmias and other autonomic disturbances as occur in epilepsy, traumatic brain injury, and genetic cardiac conditions. In general, the rostral ventral lateral medulla is a principal site of sympathetic activation, sending presympathetic neurons to the intermediolateral cell column of the spinal cord, which projects onto the stellate ganglion. The stellate ganglion then sends postganglionic sympathetic fibers directly to cardiac myocytes, activating beta-1 adrenergic receptors. Through a G-protein coupling process, intracellular cyclic adenosine monophosphate levels and protein kinase A activity are elevated, triggering a phosphorylation cascade on multiple downstream targets including L-type calcium channel receptors, the sarcoplasmic reticulum, and slow-delayed potassium channels. The outcome is an influx of calcium causing increased myocardial contractility, as well as a shortening of the myocardial action potential that promotes chronotropy.

When the blood pressure is low, baroreceptor activity from the aortic arch and carotid sinuses is diminished. This signal is relayed to the solitary nucleus of the medulla, which decreases activation of the caudal ventrolateral medulla and increases activity of the rostral ventral lateral medulla. A heightened sympathetic cardiovascular response ensues. Conversely, when blood pressure is elevated, increased baroreceptor activity inhibits the rostral ventral lateral medulla, resulting in an attenuated sympathetic response. Direct parasympathetic influences on cardiac function can also occur through excitatory neurons in the nucleus ambiguus and dorsal motor nucleus of the vagus nerve, which synapse with postganglionic neurons in the intrinsic cardiac ganglia. Acetylcholine activation of the cardiac muscarinic receptors reduces myocyte contractility and decreases the heart rate.

Genetic imbalances in the autonomic control of cardiac function can lead to life-threatening conditions. In catecholamine polymorphic ventricular tachycardia (CPVT), mutations in the cardiac RYR-2 ryanodine receptor result in abnormal levels of intracellular calcium, causing arrhythmias during sympathetic stimulation from stress and exercise. Surgeons have therefore attempted sympathetic denervation of the heart by resecting the left lower stellate ganglion and parts of the thoracic ganglia. Among a cohort of 63 patients with CPVT who underwent cardiac sympathetic denervation between 1988 and 2014, the incidence of major cardiac events was reduced from 100 to 32 percent ($P < 0.001$) over a 43-month period, and the rate of associated shocks from an implanted cardioverter defibrillator declined from 3.6 to 0.6 shocks per person per year ($P < 0.001$).[1]

Paraventricular Nucleus of the Hypothalamus

In addition to the medulla, the paraventricular nucleus of the hypothalamus plays an important role in both autonomic and neurohumoral regulation of the heart. On a neural level, the paraventricular nucleus receives afferent information from the solitary nucleus, and transmits efferent signals to the rostral ventral lateral medulla to regulate sympathetic activity. Overactivation of this sympathetic outflow has been implicated in the pathology of ischemic heart failure, particularly in chronic settings. By inhibiting activity of the paraventricular nucleus in mice, researchers have demonstrated reduced peri-infarct apoptosis and improved cardiac recovery after myocardial infarction, highlighting the link between the hypothalamus and cardiovascular function.[2] Electrical stimulation of the hypothalamus has also been associated with cardiac arrhythmias, with sympathetic regions located posteriorly, and parasympathetic areas anteriorly.

On an endocrine level, the paraventricular nucleus is involved in the stress response of the hypothalamic–pituitary–adrenal axis by secreting corticotropin-releasing factor into the portal system. This stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary lobe. Elevations in ACTH increase serum cortisol levels, which can contribute to a multitude of long-term cardiovascular complications, including hypertension, obesity, and insulin resistance.

The Limbic System and Amygdala

Emotional stimuli such as fear and anxiety can trigger autonomic responses related to the central nucleus of the amygdala. Sitting deep within the medial temporal lobes, the amygdala receives information from the prefrontal and orbitofrontal regions and sends projections to brainstem areas involved in autonomic control, thereby mediating the cardiac response to emotion. Chronic stress has been associated with cardiovascular disease, but the mechanism by which the brain is involved is poorly understood. In 2017, Tawakol and co-workers studied 293 patients with imaging techniques and found that higher levels of resting amygdalar activity predicted the risk of developing future cardiovascular events, including myocardial infarctions and unstable angina, independent of baseline cardiovascular risk. The higher levels of amygdalar activity were also associated with increased bone-marrow activity and arterial inflammation. One hypothesis is that amygdala-mediated stress increases the production of inflammatory cytokines from the bone marrow, triggering a cascade of downstream arterial inflammation leading to cardiovascular disease.[3]

Functional magnetic resonance imaging (fMRI) has now elucidated a complex network of regions involved in cardiac control. By having subjects complete tasks to elicit autonomic responses, and observing heart rate variability together with fMRI data, researchers have identified both cortical (prefrontal area, insula, anterior cingulate) and subcortical (amygdala, hypothalamus, hippocampus formation) structures involved in autonomic regulation. Moreover, sympathetic activity has been shown to localize to the prefrontal region, anterior cingulate, right anterior insula, and the left posterior insula, whereas parasympathetic activity is derived from the posterior cingulate and lateral temporal cortices, hippocampal formation, and bilateral dorsal insula. The left amygdala also contains features of both sympathetic and parasympathetic activity. This topography in function may help explain the variety of cardiac manifestations seen after ischemic injury to the brain, ranging from alterations in blood pressure to heart rate variability and arrhythmias.[4]

Insular Cortex

The insular cortex has widespread connectivity with areas of the brain that are known to be involved in autonomic control. Injury to this region has been associated with increased renal sympathetic nerve activity, elevated norepinephrine levels, and adverse cardiac events including QT prolongation, abnormal repolarization, tachycardia/bradycardia, and new-onset atrial fibrillation. Historically, it was believed that greater sympathetic representation occurred in the right insula and more parasympathetic representation featured on the left. This led to speculation that left-sided insular strokes manifested with increased and often unchecked cardiac sympathetic tone, resulting in worse cardiac outcomes, arrhythmias, and even sudden death. By contrast, however, it has also been argued that the morbidity and mortality of patients is higher among those with right-sided insular strokes, especially in the context of ECG abnormalities. The clinical significance of laterality in insular involvement remains controversial.

Using voxel-based lesion mapping on MRIs, a study in 2017 revealed that injury to the dorsal-anterior aspect of the insula was associated with elevations in cardiac troponin and myocardial damage. This suggests that in addition to the classic right-to-left grouping of insular injury, there also exists a ventral-to-dorsal subdivision that plays an equally important role in autonomic function. Ischemic injury to the dorsal anterior insula impairs parasympathetic tone, despite being on the sympathetically associated right side.[5] Indeed, conflicting observational outcomes in patients with insular strokes may well be attributed to the heterogeneity of autonomic mapping on the insular structure itself.

MECHANISM OF NEUROCARDIOGENIC INJURY

Myocardial infarction in the setting of acute stroke is not uncommon, and often represents concomitant coronary artery disease (CAD) in older patients with ischemic stroke and vascular risk factors. However, evidence from autopsy series in both ischemic and hemorrhagic stroke indicates that cardiac dysfunction may occur in the absence of underlying CAD. The Troponin Elevation in Acute Ischemic Stroke (TRELAS) study in 2015 identified 29 ischemic stroke patients with elevated cardiac troponin levels (median 95 ng/L, IQR 48–227), who simultaneously underwent diagnostic coronary angiography. Of the 29 patients, only seven (24%) were found to have a coronary culprit lesion and only 15 (51%) had obstructive CAD at all. These rates were significantly less compared to a control population of patients with non-ST elevation acute coronary syndrome and similar troponin levels.[6] Evidently, when myocardial tissue injury is present, suspicion for underlying cardiac disease increases, but such studies suggest a mechanism of injury distinct from large coronary artery–induced ischemia. Subendocardial hemorrhages described in patients dying after acute strokes and seizures also suggest pathologic changes to the heart that may be associated with neurologically mediated dysfunction. Here, we describe a commonly proposed mechanism for neurocardiogenic injury known as the catecholamine surge hypothesis.

Catecholamine Surge on Cardiomyocytes

It has been speculated that during neurologic injury, increased sympathetic activity triggers a massive release of catecholamines directly at the myocardial nerve endings. Myocardial tissue adjacent to these nerve endings is thereby vulnerable to excitatory damage. Excessive binding of catecholamines to the beta-receptors on cardiomyocytes leads to an abnormal influx of intracellular calcium, resulting in electrical instability, abnormal myocyte contraction, and oxidative stress. These processes then converge into cardiac injury in the form of arrhythmogenesis, coagulative myocytolysis, and microvascular dysfunction.

Histologically, catecholamine-induced subendocardial lesions include scattered foci of swollen myocytes surrounded by infiltrating monocytes, interstitial hemorrhages, and myofibrillar degeneration. Collectively, these pathologic changes have been called contraction band necrosis or coagulative myocytolysis (Fig. 10-1). The pattern of myofibrillar necrosis localizing near cardiac nerves is identical to other lesions thought to be of sympathetic origin such as catecholamine infusion, "voodoo death," hypothalamic stimulation, or reperfusion of transiently ischemic cardiac muscle. In patients with CAD, myocardial necrosis typically follows a vascular distribution where timing of injury occurs in a delayed fashion after progressive ischemia and muscle cell death. In neurogenic myocytolysis, however, myocardial damage can be visible within minutes of onset, with appreciable differences observed on a cellular level that include mononuclear infiltration, early calcification, and a hypercontracted state of myocardial cells.

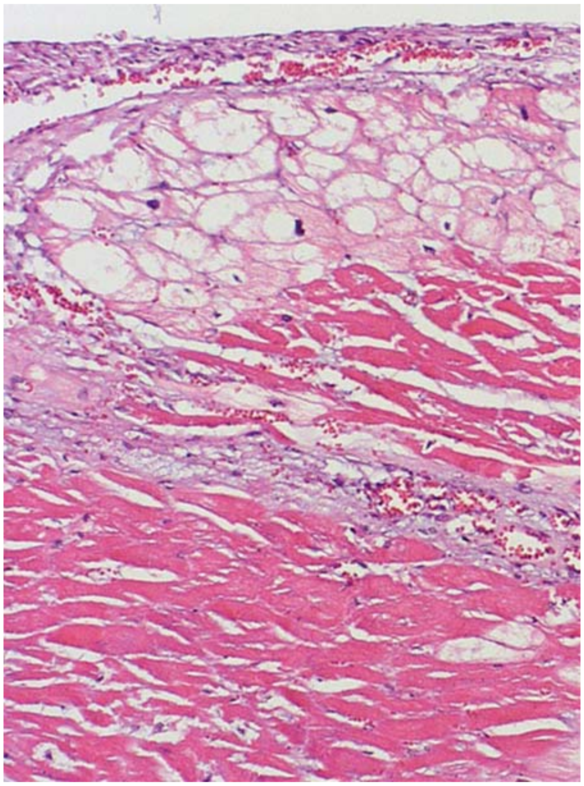

FIGURE 10-1 ■ A representative cross-section of myocardium after hematoxylin–eosin stain showing marked myocyte hypertrophy with nucleomegaly, and myocytolysis. (Courtesy of Dr. Philip Ursell, MD.)

Experimental and clinical studies have addressed the neurogenic catecholamine-mediated mechanism of cardiac dysfunction. In a cohort of patients with SAH who had echocardiograms and nuclear scans of cardiac innervation and perfusion, regions of contractile dysfunction were associated with abnormalities in myocardial sympathetic innervation while cardiac perfusion was normal. The degree of cardiac innervation was measured with a scintigraphic evaluation using [^{123}I]metaiodobenzylguanidine (MIBG), cardiac perfusion was measured using [^{99m}Tc]sesta-methoxyisobutylisonitrile (MIBI), and regions of myocardial dysfunction were determined by echocardiography simultaneously in the patients. Patients with functional cardiac denervation had worse regional wall motion scores and more troponin release than patients without evidence of cardiac denervation. Fig. 10-2 illustrates normal perfusion and global denervation in a patient with SAH whose echocardiogram showed global left ventricular systolic dysfunction. All study subjects had normal perfusion imaging, which excluded significant CAD and supported a neurogenic mechanism of cardiac injury.[7]

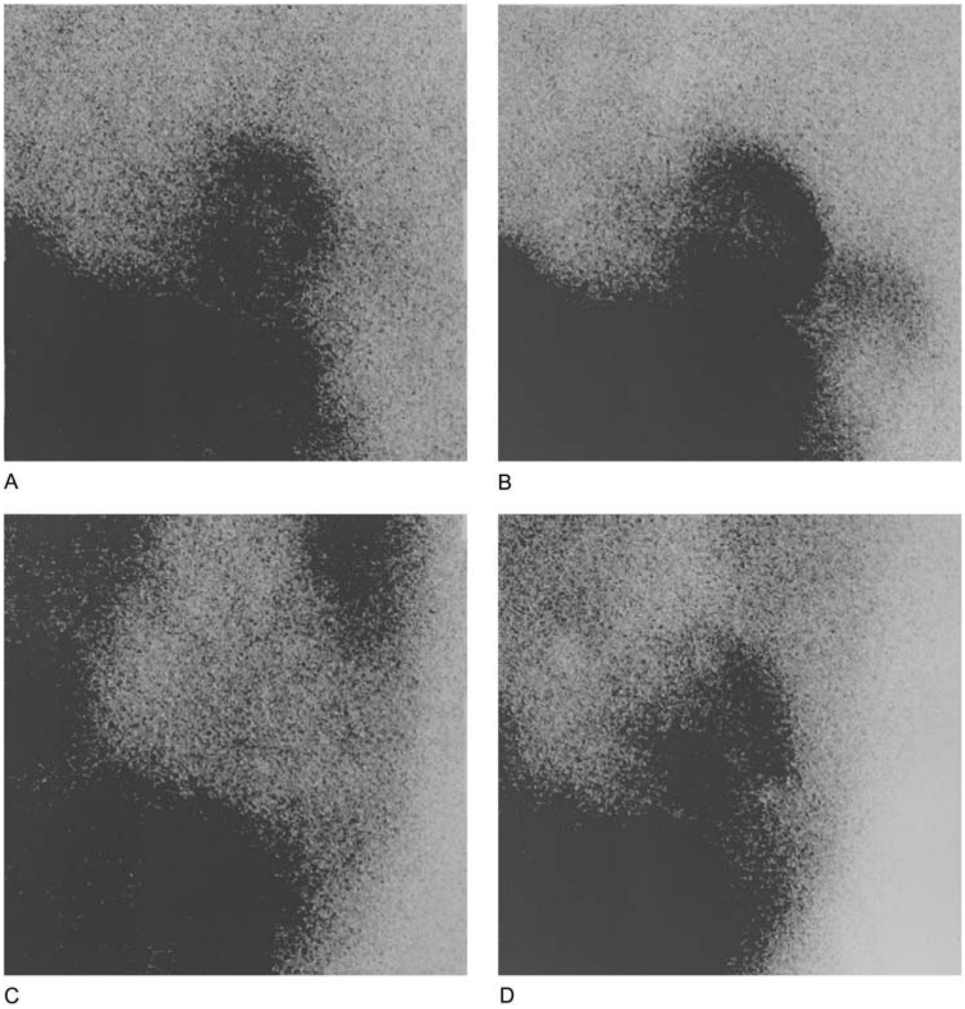

FIGURE 10-2 ■ Normal myocardial innervation, *A*, and perfusion, *B*, in a 71-year-old man with SAH. Global functional denervation, *C* and normal perfusion, except for a nonspecific apical irregularity, *D*, in a 41-year-old woman with SAH. (From Banki NM, Kopelnik A, Dae MW, et al: Acute neurocardiogenic injury after subarachnoid hemorrhage. Circulation 112:3314, 2005, with permission.)

Catecholamine Surge on Coronary Microvasculature

Despite the evidence for a neurologically mediated mechanism of cardiac impairment independent of CAD, there is also evidence to support a centrally mediated source of injury to the coronary microvasculature. During SAH, the body's stress response leads to elevated levels of cortisol (via the hypothalamic–pituitary–adrenal axis), endothelin/angiotensin II (via neurohumoral responses), and circulating catecholamines (via the adrenal medulla). Together, these factors incite peripheral vascular constriction and induce coronary microvascular spasm, contributing to demand ischemia of the heart. Catecholamines and endothelin bind directly to α_1-receptors and endothelin A receptors on the coronary microvasculature, respectively, which leads to vasoconstriction and a reduction in coronary blood flow. In Takotsubo cardiomyopathy, which can be seen after SAH, studies have shown increased plasma levels of the vasoconstricting peptide, endothelin-1, as well as decreased expression of the endothelin-1 regulating miRNA 125a-5p, when compared to healthy controls.[8] Delivery of intravenous adenosine, a potent vasodilator, has also been shown transiently to improve left ventricular function and myocardial perfusion in patients with Takotsubo cardiomyopathy, as compared to patients with ST-elevation myocardial infarctions.[9] As a result, these studies support the hypothesis that microcirculatory vasospasm may be a cause of transient cardiac injury and is potentially driven by the neurohumoral and catecholaminergic responses to neurologic injury.

CARDIAC MANIFESTATIONS OF GLOBAL NEUROLOGIC INJURY

Reduced Left Ventricular Function

Much of the evidence for a neurogenic mechanism of cardiac injury comes from studies of cardiac function after SAH, which typically affects younger patients without a history of co-existent cardiac disease. Global or regional left ventricular systolic dysfunction on echocardiogram has been described after SAH and is strongly associated with the severity of neurologic injury. Diastolic dysfunction is also common after SAH, is similarly associated with the severity of neurologic injury, and may cause pulmonary edema. The onset of left ventricular dysfunction occurs early after SAH. In a large prospective study, a regional wall motion abnormality was observed in 28 percent, and global left ventricular dysfunction in 15 percent of patients with SAH, all of which was present within the first 2 days.[10] The prevalence then declined during days 3 to 8 after hemorrhage. In this same study, the authors demonstrated complete or partial resolution of left ventricular dysfunction in the majority of patients during their acute hospitalization. Thus, cardiac dysfunction appears to be reversible in most cases and normalizes over time.

Regional Wall Motion Abnormalities

There is a well-demonstrated, unique, apical-sparing pattern of regional wall motion abnormality, often involving the anterior and anteroseptal walls, that differentiates SAH patients from those with the typical patterns seen in CAD. The presence of wall motion abnormalities in SAH is not only a predictor of adverse clinical outcomes, but has also been associated with the increased incidence of delayed cerebral ischemia.[11] Given that patients with SAH have impaired cerebral autoregulation and are at risk of vasospasm and hypovolemia, it is speculated that wall motion abnormalities impair overall cardiac output, thereby reducing cerebral perfusion and causing delayed cerebral ischemia. Apical wall motion abnormalities with hyperdynamic basal contractility suggestive of Takotsubo cardiomyopathy can also be seen in SAH, with an increased predominance in females and insular involvement. In both patterns of injury (apical-sparing and Takotsubo cardiomyopathy), the wall motion abnormality does not follow a distinct vascular distribution, thereby reinforcing the notion of a neurally mediated process. In 2019, researchers investigating resting-state functional connectivity on fMRIs found that decreased baseline connectivity in the limbic–autonomic pathways of the brain was associated with Takotsubo cardiomyopathy. While it remains difficult to ascertain the causal relationship of such findings, it is possible that the inherent limbic–autonomic reserve of certain patients makes them more vulnerable to maladaptive sympathetic responses after neurologic insults, resulting in cardiac impairment.[12]

Cardiac Biomarkers of Neurologic Injury

Creatine Kinase-MB

In addition to pathologic data and measurements of cardiac function, elevations in cardiac enzymes provide evidence of myocardial injury after stroke and SAH. Creatine kinase (CK) and specifically the cardiac isoenzyme CK-MB are released from damaged myocardium. Elevated serum levels can occur after both stroke and SAH, and there is a good correlation between elevation in CK-MB and stroke-induced ECG changes or cardiac arrhythmias. Unlike acute myocardial infarction, a stroke-induced increase in serum CK-MB levels occurs more slowly and peaks at a much lower value on around day 4 after stroke.

Troponin

Cardiac troponin I is a specific and more sensitive marker of myocardial damage. Elevations in troponin I have been described in up to 30 percent of patients with SAH, with stepwise increases in levels correlated to the severity of initial injury (i.e., Hunt Hess score). SAH patients with elevations in troponin have higher rates of prolonged QTc on ECGs, more frequent ventricular tachycardia on Holter monitoring, and features of impaired LV function and regional wall motion abnormalities, as compared to those without troponin elevations. Such cardiac manifestations are associated with increased mortality, poorer functional outcomes, and delayed cerebral ischemia.[11,13] A rise in cardiac troponin is similarly seen in acute ischemic strokes. Of the 2123 consecutive patients with ischemic strokes in the TRELAS study, 13.7 percent were found to have cardiac troponin levels greater than 50 ng/L. Among these patients, a predefined subset subsequently underwent coronary angiography, with less than a quarter of the patients showing a coronary lesion, and only half showing any features of CAD at all.[6]

B-Type Natriuretic Peptide

Serum B-type natriuretic peptide (BNP) is often used as a marker of heart failure. Elevated serum BNP levels after SAH have been independently associated with systolic and diastolic dysfunction, pulmonary edema, elevated troponin I levels, and lower cardiac ejection fractions. The predominance of cardiac abnormalities similar to heart failure suggests that although BNP is found in heart and brain, elevated levels are likely to be of cardiac origin. Moreover, elevated troponin I and BNP levels are independent and strong predictors of inpatient mortality after SAH and may have a similar link to mortality in acute ischemic stroke as well.

CARDIAC MANIFESTATIONS OF FOCAL NEUROLOGIC INJURY

Clinical observations in patients with stroke have greatly advanced the understanding of interactions between the brain and heart. Cardiac abnormalities occur in a majority of patients after stroke, and can range from transient ECG findings to serious cardiac events and cardiac death. Distinguishing cardiac abnormalities caused directly by stroke, however, remains difficult because of the high prevalence of pre-existing cardiac disease. Substantial evidence supports the occurrence of new cardiac disturbances after stroke, even in the absence of significant CAD. Epidemiologic evidence supports the presence of stroke as a significant contributor to absolute risk estimates for outcomes of vascular disease, including risk of myocardial infarction and cardiac causes of death. Understanding the mechanisms of cardiac disturbances may prevent future cardiac complications and improve survival in stroke patients.

Electrocardiographic Findings

ECG abnormalities are common, presenting in the majority of patients with acute stroke. Historically, an ECG pattern after acute stroke consisting of large inverted T waves, prolonged QT intervals, and large septal U waves has become distinctive of cerebrovascular injury (Fig. 10-3). Abnormal ECGs are most frequently observed after hemorrhagic rather than ischemic strokes, even in patients who never had an abnormal ECG prior to the stroke event. A variety of abnormalities have been described including ST depression, prolongation of the QT interval, T-wave inversion, and ventricular premature beats. Studies suggest that ECG abnormalities can occur with or without co-existing heart disease.

QT Prolongation

The most common stroke-related ECG abnormality is QT prolongation, a myocardial repolarization abnormality associated with an increased risk of a characteristic life-threatening cardiac arrhythmia, known as torsades de pointes (Fig. 10-4). Interestingly, imbalance of the sympathetic innervation of the heart has been described in congenital forms of long QT syndrome, suggesting a common mechanism with the catecholamine hypothesis described earlier. Prolonged QT interval is more frequently observed after hemorrhagic than ischemic strokes. Early recognition of this ECG abnormality is clinically important because ventricular tachyarrhythmias including sudden death and torsades de pointes are often preceded

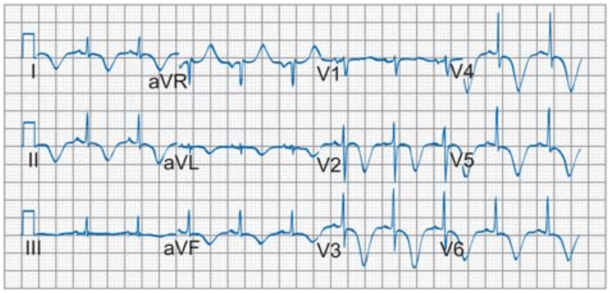

FIGURE 10-3 ■ Typical "neurogenic" electrocardiographic changes with symmetric deep T-wave inversions in a patient with acute subarachnoid hemorrhage. These abnormalities were transient and not associated with myocardial infarction. (Courtesy of Dr. Jonathan Zaroff, MD.)

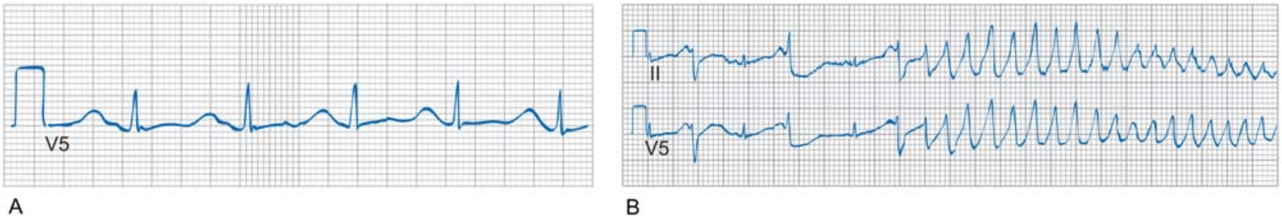

FIGURE 10-4 ■ Electrocardiographic (ECG) changes can precede pathologic arrhythmias in patients with severe neurologic injuries. *A*, Prolongation of the QT interval is common after subarachnoid hemorrhage. Electrolyte abnormalities or medications can also prolong the QT interval. *B*, Torsades de pointes is a polymorphic ventricular tachycardia associated with QT prolongation. (Courtesy of Dr. Byron Lee, MD.)

by QT prolongation. Assessment and management of common causes of these ECG changes, such as hypokalemia, hypomagnesemia, and medication toxicity, is recommended before attributing them to the underlying stroke.

REPOLARIZATION ABNORMALITIES

The similarities between ECG changes due to acute myocardial ischemia and infarction and those associated with acute stroke are most striking with repolarization abnormalities involving the ST segment, leading many investigators to hypothesize co-existing cardiac disease as the primary cause. Interpretation of ST segment changes (including ST elevations) is complicated by the increased prevalence of cardiac disease among ischemic stroke patients. However, studies have shown new T-wave abnormalities after acute stroke in the absence of electrolyte disturbances or primary ischemic heart disease (as determined by detailed cardiac assessments including echocardiogram and cardiac angiography). These findings, along with the observation that stroke-induced ECG changes are evanescent, resolving over a period of days to months with little residuum, argue against myocardial ischemia or infarction as the only cause of repolarization changes on ECG.

Q WAVES AND U WAVES

New Q waves similar in morphology to those observed in acute myocardial infarction are also common after acute stroke. To complicate matters, Q waves may be transient or proceed through the evolutionary changes seen in myocardial infarction. Further cardiac evaluation may be necessary in high-risk patients with Q waves and ST segment alterations, particularly if they are over 65 years of age with coronary risk factors such as diabetes mellitus, hypertension, and hyperlipidemia.

New U waves occur in isolation or with T waves and QT abnormalities after acute stroke. Isolated U waves are equally distributed between ischemic and hemorrhagic strokes, but the combination of U waves and QT prolongation is more common among patients with hemorrhagic strokes. There is no relationship between the presence of U waves and stroke mortality, suggesting that this ECG change should not require any specific treatment or evaluation.

Disturbances of Cardiac Rhythm

ARRHYTHMIAS

Nearly every type of cardiac arrhythmia has been reported after acute stroke, including bradycardia, supraventricular tachycardia, atrial flutter, atrial fibrillation, ectopic ventricular beats, multifocal ventricular tachycardias, torsades de pointes, ventricular flutter, and ventricular fibrillation. Most arrhythmias occur within the first week after all stroke subtypes, particularly in the first 24 hours. Atrial fibrillation is the most common cardiac arrhythmia reported after ischemic stroke. Not surprisingly, since the ECG is a relatively insensitive test for arrhythmia, a higher incidence of ventricular extrasystoles, atrial extrasystoles, supraventricular tachycardia, and atrial fibrillation can be captured using cardiac telemetry monitoring. Importantly, the presence of arrhythmias after stroke is significantly associated with increased mortality, and guidelines recommend cardiac monitoring in hospitalized stroke patients during the first 72 hours. Newer literature supports extended cardiac event monitoring for cryptogenic embolic strokes.

In studies of hemorrhagic strokes, the incidence of ventricular arrhythmias is higher. Location of hemorrhage appears to correlate with the rhythm disturbances. Ventricular arrhythmias are correlated with temporoparietal location, whereas sinus bradycardia and supraventricular tachycardias are seen more commonly with traumatic frontal lobe hemorrhage.

Patients with SAH may have even more profound rhythm disturbances that may be related to the diffuse nature of the injury and the degree of monitoring in the intensive care unit. Because the frequency and severity of arrhythmias are significantly higher in patients studied within 48 hours of onset of SAH, we recommend continuous cardiac monitoring in an intensive care setting for all such patients.

HEART RATE VARIABILITY AND BARORECEPTOR REFLEX SENSITIVITY

During the acute phase after ischemic stroke, autonomic dysfunction can present with decreased heart rate variability and impaired baroreflex sensitivity, particularly among patients with higher stroke scale severity, right insular involvement, and carotid injury. Decreased heart rate variability correlates with short-term mortality and sudden cardiac death, and patterns of beat-to-beat variability have been used to predict which patients will go on to develop neurocardiogenic injury after SAH.[14] Similarly, impaired baroreflex sensitivity is thought to reflect a pathologic shift toward sympathetic predominance leading to dynamic fluctuations in blood pressure. Although not fully understood, impaired baroreflex sensitivity has predictive value in both cardiac and neurologic conditions, including mortality after myocardial infarction, perihematomal edema size after ICH, and the incidence of malignant cerebral edema after infarcts in the territory of the middle cerebral artery.[15] One hypothesis involves a stroke-induced decoupling of cerebrovascular autoregulation, thereby making the brain vulnerable to wide fluctuations in blood pressure, which, in turn, trigger local inflammation and edema formation.

EPILEPSY AND TRAUMA

Similar cardiac arrhythmias and ECG findings have been described in patients with epilepsy, brain tumors, head trauma, meningitis, multiple sclerosis, and spinal lesions. In all cases, a common mechanism of neurogenic cardiac injury is supported by increased sympathetic nervous system discharge and increased catecholamine production by the adrenal medulla. Analogous to SAH, patients with chronic temporal lobe epilepsy may have baseline dysfunction in cardiac sympathetic innervation with normal myocardial perfusion scans.

Epilepsy

Sinus tachycardia is by far the most common cardiac manifestation during epileptic seizures, occurring in up to 90 percent of instances and present in both clinical and subclinical events. The increase in heart rate typically occurs at ictal onset, followed by variable heart rate patterns thereafter. Cardiac arrhythmias in the form of asystole, atrioventricular block, and bradycardia may also be present in seizures, with contrasting mechanisms between the ictal and postictal phases. During the ictal period, there is a sudden release of catecholamines triggered by cortical discharges often arising in regions of the insula. This sympathetic surge, as seen with sinus tachycardia, can be followed by a centrally mediated vasovagal response, with rebound parasympathetic activity causing bradyarrhythmias. As the arrhythmias persist, cerebral perfusion declines and the ictal onset aborts, stimulating arousal. This process may explain the self-limiting properties of ictal asystole, and its lack of association with long-term complications. Arrhythmias during the ictal phase are more frequently seen with focal seizures involving the temporal lobe, but the laterality of onset remains controversial.

In contrast, postictal arrhythmias such as postictal asystole and AV block are more associated with convulsive seizures, and thought to play a role in the phenomenon of sudden unexpected death in epilepsy (SUDEP).[16] In 2013, the MORTEMUS study analyzed continuous cardiac rhythms of 16 patients who developed SUDEP in epilepsy monitoring units across multinational centers. The findings demonstrated for the first time a sequential mechanism of convulsive seizures, followed by central apnea, bradycardia, and eventually asystole. During these events, there was also a concomitant pattern of prolonged postictal generalized EEG suppression, reflecting a "postictal coma." One theory is that during central apnea, the body's chemoreceptor response not only induces bradycardia, but also facilitates arousal and resumption of ventilation. When this arousal is blocked by "postictal coma," ventilation remains impaired and prolonged bradycardia and asystole ensue. This mechanism of injury leads to a potentially fatal cardiovascular collapse, occurring in both an acute and delayed fashion. In the MORTEMUS cohort, the incidence of SUDEP was estimated to be about 5.1 cases per 1,000 patient-years, with increased incidence during the nocturnal period.[17] The risk of sudden unexpected death has previously been related to increased seizure frequency, generalized seizures, younger age, lower concentration of antiepileptic medications, use of multiple medications, and duration of epilepsy.

Long-term cardiac monitoring with implantable loop recorders suggests that ictal and postictal bradyarrhythmias may be more common than previously supposed. Other types of arrhythmias seen during or after epileptic seizures include atrial flutter, atrial fibrillation, and ventricular tachycardia/fibrillation.

Traumatic Brain Injury

Paroxysmal sympathetic hyperactivity (PSH) is a term coined to describe the excessive sympathetic response seen in patients with severe traumatic brain injury, which occurs in 8 to 33 percent of patients. In this hyperdynamic cardiac state, paroxysmal clinical symptoms are triggered by external stimuli, and include tachycardia, tachypnea, hypertension, hyperthermia, diaphoresis, tremors, dystonic posturing, and decreased levels of consciousness—all of which portend worse clinical outcomes. PSH may begin within 2 weeks of the neurologic insult and persist for as long as several months. Although its underlying pathophysiology remains unknown, it is postulated to involve a disconnect of the brainstem nuclei and their inhibitory pathways to the spinal interneurons modulating spinal reflex arcs. This results in a maladaptive reaction to afferent sensory stimuli that induces an overactive spinal circuit excitatory response, leading to increased motor and sympathetic output. The periaqueductal gray matter is believed to play a key role in the supraspinal inhibitory control of this mechanism.[18] Thus, midbrain lesions have been implicated in the manifestation of PSH.

Risk factors for PSH include younger age, presence of diffuse axonal injury, and lesions to white matter tracts. As previously described, the balance between sympathetic and parasympathetic activity in the brain is also regulated by communication between the cortical (i.e., insula, cingulate gyrus) and subcortical structures (i.e., amygdala, hypothalamus, medulla). Damage to this network during trauma, as seen with diffuse axonal injury and shear injury to the white matter tracts, may contribute to the dysregulation of autonomic responses in PSH, in addition to any involvement of the periaqueductal gray matter.

Treatment for PSH focuses primarily on reducing the provoking stimuli and dampening the sympathetic outflow. This usually involves opioid analgesia and benzodiazepines as first-line treatment, followed by β-blockers, gabapentin, α-blockers, and bromocriptine. Although such medications afford symptomatic relief, no treatments have proven effective in improving outcomes in patients with PSH after traumatic brain injury.

CARDIAC EVALUATION

Proper evaluation of cardiac injury and dysfunction remains important for both cardiac and neurologic prognosis. Patients with ischemic stroke, in particular, are more likely to have concomitant significant CAD. A strong association between cerebrovascular disease and CAD has been established in a number of clinical studies, with nearly half of patients with TIAs or ischemic stroke showing CAD on coronary angiography or on functional testing with thallium stress images. Given the higher probability of CAD, several diagnostic evaluations are recommended in the acute period for all patients with ischemic stroke including an ECG and measurement of serum troponin I levels. Further functional testing with echocardiogram and continuous cardiac monitoring are often initiated to determine the risk of a cardiogenic source of embolic ischemic strokes. Exercise or pharmacologic stress test (nuclear or echocardiographic) and coronary angiogram should be obtained based on the patient's risk level and functional status.

The majority of patients with acute stroke will not be considered for acute treatment for myocardial infarction, but coronary angiography may be indicated if there is a strong clinical suspicion of plaque rupture or thrombus formation that may be safely treated endovascularly. As previously described, distinguishing cardiogenic from neurogenic causes of myocardial injury can be problematic. Evaluation for clinical signs of heart failure, such as cardiogenic pulmonary edema and hypotension, careful analysis of the ECG, assessment of cardiac function by echocardiogram, and evaluation of myocardial necrosis by cardiac markers may help to determine the need for cardiac catheterization. The serum CK-MB levels are insensitive and should not be used for differentiation between neurogenic and cardiogenic injury. A large increase in serum troponin I levels with a significant temporal trend, along with ECG changes that correlate with the location of left ventricular systolic dysfunction on echocardiogram, may be more suggestive of CAD. In contrast, common neurogenic ECG changes, including T-wave inversion, QTc prolongation, a shorter PR interval, and the presence of U waves, may aid in differentiating neurogenic injury from myocardial infarction.

In hemorrhagic strokes, the frequency of cardiac arrhythmias is high and often correlates with ECG changes. Baseline ECG and continuous cardiac monitoring in this population are often performed in the intensive care unit. Patients with SAH pose a greater challenge when the complication arises of cerebral vasospasm and delayed cerebral ischemia. Unless contraindicated, the typical management of these patients may include induced hypertension with pressors to improve cerebral blood flow through narrowed vasculature. SAH patients could potentially benefit from measurement of serum troponin I and BNP levels as well as a transthoracic echocardiogram as part of their initial management. A close, independent relationship has been established between the severity of SAH and the probability of troponin release, and could be used to anticipate greater risk of cardiac abnormalities in these patients. Coronary angiography after SAH is generally not recommended because most patients with left ventricular dysfunction following SAH who undergo cardiac catheterization have normal epicardial coronary arteries and no evidence of large coronary vasospasm.

For patients with epilepsy, sudden unexpected death is the most feared complication. Growing evidence suggests that neurogenic cardiac arrhythmias may contribute to the risk of sudden death. Identifying patients at highest risk of this complication has been challenging. In addition to clinical risk factors and promoting better compliance with medication, advanced cardiac monitoring with ambulatory ECG and long-term implantable loop recorders may help to identify patients with pathologic arrhythmias. In addition, other methods for measuring cardiac autonomic input, such as heart rate variability and spectral analysis, may be useful.

In patients with traumatic brain injury, continuous cardiac monitoring in the intensive care unit often detects heart rate and blood pressure variability and, combined with multimodality monitoring, can correlate changes associated with elevations in ICP and cerebral perfusion pressure. Incorporating measurements of heart rate variability may also be useful for prognosis.

CLINICAL MANAGEMENT

After identification of the common cardiac abnormalities, management should be initiated to prevent their detrimental effect on patient outcomes. The most common ECG changes generally do not require specific treatment, but may prompt further testing and continuous monitoring. Identification of other causes or contributors to ECG changes can lead to rapid resolution. In particular, specific treatment of hypokalemia, hypomagnesemia, and medication toxicity may correct a prolonged QT interval. Antiarrhythmic (e.g., quinidine, sotalol, amiodarone) or antipsychotic drugs (e.g., haloperidol) known to affect the QT interval should be avoided in these patients, especially if their neurologic injury exacerbates underlying hereditary long QT syndrome. When repolarization abnormalities occur, it may be necessary to exclude acute myocardial infarction. Common electrolyte abnormalities such as hyperkalemia can produce tall T waves, whereas hypokalemia is the most common cause of U waves. Correction of electrolyte abnormalities may reduce the risk of arrhythmias.

Cardiac rhythm disturbances after neurologic injury can be complex, requiring cardiology consultation. The most important aim is to identify patients who may be hemodynamically unstable in the presence of an arrhythmia. This is a medical emergency and should be managed immediately by appropriate personnel in the intensive care unit, with the involvement of a cardiac team. In a stable, asymptomatic patient, identifying the type of arrhythmia can guide management. Atrial or ventricular premature contractions generally do not require specific treatment. For sinus bradycardia or tachycardia, identification and treatment of the common underlying conditions, such as fever, thyroid dysfunction, anemia, pain, sepsis, and anxiety, will often correct the rhythm disturbance.

Specific pharmacologic treatment may be required if the patient develops stable tachyarrhythmias. A trial of adenosine can terminate supraventricular tachycardia and assist in determining the underlying rhythm disturbance. Rate control with an intravenous β-blocker, calcium-channel blocker, or amiodarone can be used in patients with atrial fibrillation or flutter, most common after ischemic stroke and ICH. Stable ventricular tachyarrhythmias can also be managed with intravenous amiodarone or lidocaine. Specific treatment of torsades de pointes includes intravenous magnesium. Any arrhythmia more complex than ectopic beats or sinus bradycardia or tachycardia should prompt a cardiology consultation.

When more significant cardiac dysfunction or injury is identified by elevated serum markers or dysfunction on ECG, several steps can be taken to improve cardiac prognosis. If CAD is present, management of atherosclerosis risk factors (diabetes, hyperlipidemia, hypertension, and smoking) and treatment with antiplatelet agents and lipid-lowering agents may help both the ischemic stroke and heart disease. The β-blockers reduce the risk of vascular events after myocardial infarction, but their role in the prevention of cardiac events in other high-risk patients with stroke is unclear. Finally, revascularization by angioplasty or coronary artery bypass grafting is beneficial for patients with symptomatic CAD, but the decision to treat must balance the risk to the patient with an acute neurologic injury.

In the rare event of coronary plaque rupture in a patient with SAH, coronary angioplasty along with stenting may be considered once the aneurysm is secured and the necessary anticoagulation regimen can be tolerated safely. Although further studies are needed to determine the safety of percutaneous coronary intervention and anticoagulation after successful aneurysmal intervention, patients with unsecured aneurysms should not undergo any coronary intervention given the unacceptably high risk of rebleeding.

In patients with SAH, the presence of cardiac injury and dysfunction often directly affects management. The decision to treat a ruptured aneurysm should not be delayed because of concerns regarding cardiac injury. Because the mechanism of neurogenic cardiac injury is probably mediated by catecholamines, treatment should focus on correcting or improving the underlying neurologic process. Prevention of rebleeding with early aneurysm clipping or endovascular coiling has proved beneficial, but selection of treatment modality may be influenced by cardiac risk.

Management of cerebral vasospasm in the setting of significant neurocardiogenic injury is challenging and directly impacts neurologic prognosis. Permissive hypertension requiring pressors to improve cerebral blood flow often leads to increased myocardial wall stress and oxygen consumption. Although most patients tolerate treatment for cerebral vasospasm, selection of the most appropriate vasopressor agent must take underlying cardiac function into account. Phenylephrine, a commonly used pressor in the intensive care unit, is predominantly an alpha-1 agonist that increases systemic vascular resistance, and thus may worsen cardiac output in those with a poor ejection fraction. Studies have suggested the use of alternative positive inotropic agents such as norepinephrine, dobutamine, and milrinone, which may be more effective at improving cerebral perfusion pressure in patients with low cardiac output. In those patients with diastolic dysfunction, attention to volume status is important as hypervolemia may cause increased filling pressures, leading to pulmonary edema. In patients with severe neurogenic cardiac injury and evidence of heart failure who are unable to tolerate medical therapy for delayed cerebral ischemia, placement of an intra-aortic balloon pump to increase cerebral perfusion pressure has been successful.

Given the potential role of excessive catecholamines in neurocardiogenic injury, β-blockers may have a role in providing cardioprotection if administered early in the hospital course, but supporting evidence is limited and based on small studies. Pathologic correlation suggests that β-blockade may protect myocytes from the hostile environment caused by massive levels of catecholamines released from cardiac sympathetic nerve terminals following SAH. Larger studies will help to determine the role of early administration of β-blockers in patients with cardiac dysfunction following SAH. Calcium-channel blockers targeting the calcium overload preceding contraction-band necrosis have not been well studied. There does not appear to be a significant cardiac benefit from nimodipine, the calcium-channel blocker already administered to patients with SAH for vasospasm prophylaxis.

CONCLUDING COMMENTS

Cardiac disturbances are diverse and frequent in the setting of acute neurologic injury. More importantly, the presence of cardiac abnormalities has significant impact on clinical management and affects cardiac and neurologic outcomes adversely. Understanding of the underlying pathophysiology and localization of the important autonomic regulatory centers involved in brain–heart interactions has progressed significantly in recent years. Animal models have been translated into important clinical research studies that have revealed further complexity in the brain regulation of cardiac function. Early recognition and appropriate treatment interventions have already impacted clinical management and may influence treatment for prevention and improving outcomes for both the heart and the brain.

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CHAPTER

11

Stroke as a Complication of General Medical Disorders

LIRONN KRALER ■ GREGORY W. ALBERS

HYPERTENSION
BLOOD LIPIDS
DIABETES MELLITUS
HOMOCYSTEINE
CARDIAC DISEASE AND STROKE
  Atrial Fibrillation/Atrial Flutter
  Patent Foramen Ovale
WOMEN'S HEALTH AND STROKE
  Stroke in Pregnancy
  Menopause
HEMATOLOGIC DISORDERS
  Antiphospholipid Antibody Syndrome
  Sneddon Syndrome
  Factor Deficiencies
  Inherited Thrombophilias
  Sickle Cell Anemia
  Cryoglobulinemia
INFECTIONS
  Acute Bacterial Meningitis
  Tuberculous Meningitis
  Syphilis
SYSTEMIC LUPUS ERYTHEMATOSUS
ONCOLOGY AND STROKE
  Coagulopathy in the Setting of Cancer
  Nonbacterial Thrombotic Endocarditis
  Stroke Related to Cancer Therapy
  Intracerebral Hemorrhage
  Direct Tumor Effects
MIGRAINE AND STROKE
  Stroke Prevention in Migraine
DRUGS AND STROKES
  Estrogens
  Anabolic Androgenic Steroids
  Alcohol
  Tobacco
  Amphetamines
  Cocaine
  Cannabis and Cannabinoids
  Migraine Medications
GENETICS OF STROKE

Stroke broadly describes the sudden onset of neurologic dysfunction due to an abnormality of blood supply to the brain, retina, or spinal cord. Ischemic stroke makes up the majority of all strokes and is often considered synonymous with stroke although the definition extends to intracerebral hemorrhage, cerebral venous sinus thrombosis, subarachnoid hemorrhage, and retinal and spinal ischemia. In a 2013 update from the American Heart Association and the American Stroke Association, cerebral ischemia and cerebral hemorrhage that were present on brain imaging without an overt neurologic symptom (i.e., were "silent") were included in the definition of stroke to underscore the significance of the pathology regardless of clinical manifestation.[1] This definition of stroke is not widely accepted outside of the United States and will have implications for comparing outcomes and disease prevalence internationally. Cerebrovascular accident (CVA) is a related term that has fallen out of favor in part because it implies the outcome as unanticipated. On the contrary, ischemic and hemorrhagic strokes are usually not "accidents," but rather manifestations of chronic conditions.

Ischemic stroke has an association with many general medical conditions. It is a heterogeneous disorder caused by any combination of thrombosis, embolism, or hypoperfusion. Ischemic stroke etiology is commonly subtyped into broad categories including small artery (lacunar), large vessel

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atherosclerotic, or cardioembolic, and there is overlap in the medical conditions that lead to these stroke subtypes. This chapter will review the most common medical conditions that underlie stroke.

HYPERTENSION

Hypertension is the most common risk factor for ischemic stroke and is responsible for the greatest proportion of preventable strokes. The relationship between stroke and blood pressure seems to be maintained well under the traditional threshold of 140/90 mmHg, and even modest decreases in blood pressure reduce stroke risk. Elevated blood pressure exerts injury throughout the cerebrovascular system and is a risk factor for multiple types of stroke including intraparenchymal hemorrhage, aneurysmal subarachnoid hemorrhage, and ischemic stroke of multiple subtypes, including small vessel, large vessel, and cardioembolic. The mechanisms underlying each stroke type are distinct but result from a combination of mechanical and inflammatory injury to both small and large vessel artery walls. Elevated blood pressure also increases the risk of cardiac structural changes, atrial fibrillation, and myocardial infarction and therefore is an indirect but important cause of cardiac embolus formation leading to stroke.

Treatment of blood pressure is effective for both primary and secondary stroke prevention, and higher intensity strategies of blood pressure reduction are thought to have played a major role in the reduction of the population stroke risk in the United States over the past half century (see Chapter 7).

BLOOD LIPIDS

Elevated total cholesterol and low-density lipoprotein (LDL) are correlated with atherogenesis of the carotid arteries and with heart disease, while high-density lipoprotein seems to be protective. Although the correlation between atherosclerotic disease and heart disease is well known, there is little correlation between the absolute levels of serum cholesterol and LDL and ischemic stroke risk.

HMG-CoA reductase inhibitors (statins) reduce LDL by inhibiting their synthesis and are an important component of stroke prevention therapy. Although their effect can be measurable in terms of LDL reduction, it is currently believed that statin medications exert their stroke reduction via other antiatherogenic mechanisms. Ezetimibe and PCSK9 antibodies are mechanistically distinct from statins and are used as add-on therapy for further LDL reduction when required; currently, these medications are recommended for use in patients who are considered to be at high risk for atherosclerotic cardiovascular disease.

DIABETES MELLITUS

While often present with other metabolic risk factors, the presence of diabetes independently increases stroke risk (see Chapter 19). The pathogenesis may be mediated by an enhanced atherogenesis in diabetics, microvascular disease of the arterial walls, and the promotion of coagulation by way of platelet activation and changes in coagulation factors. As with hypertension, diabetes mellitus is associated with several ischemic stroke subtypes.

Hyperglycemia is associated with an increased risk of mortality following stroke, and prevention of *severe* hyperglycemia during this period confers an improved outcome. However, intensive blood glucose control in the immediate period following acute stroke (i.e., maintaining blood glucose less than 130 mg/dL) does not seem to render any benefit in stroke recovery compared to strategies that aim to prevent hyperglycemia (blood glucose greater than 180 mg/dL).

HOMOCYSTEINE

Homocysteine is an intermediate in methionine metabolism, and hyperhomocysteinemia may result from an acquired or genetic deficiency in the enzymes or co-factors involved. Elevated plasma homocysteine is associated with all-cause vascular disease, mortality, and an increased risk of ischemic stroke. High levels of homocysteine are also linked to vascular injury and atherosclerotic plaque formation.

Severe hyperhomocysteinemia results in homocystinuria and is usually caused by inborn errors of metabolism. Individuals with homocystinuria experience premature atherosclerosis, thromboembolic disease including stroke, developmental delay, osteoporosis, marfanoid appearance, and ectopia lentis. This condition is usually diagnosed prior to young adulthood due to the overt manifestations.

In contrast, mild to moderate hyperhomocysteinemia may be clinically asymptomatic and accompany vitamin deficiencies (e.g., B_{12}, B_6, folate), and genetic variants including mutations in the methylenetetrahydrofolate reductase gene (*MTHFR*). Mild to moderate elevations of homocysteine are also associated with vascular disease and ischemic stroke; however, whether mild to moderate elevations of homocysteine directly contribute to vascular injury or are merely a marker of vascular disease is debated.

Folate, B_{12}, and B_6 vitamin supplementation reduce levels of plasma homocysteine, even in the absence of overt vitamin deficiency, and have been studied for their effect on stroke reduction without much promise to date. In a 2017 Cochrane review including 15 randomized trials, 71,422 participants, and up to 7.3 years follow-up concluded that homocysteine-lowering interventions had a possible but small reduction in stroke risk.[2] In combination with antihypertensive medications, homocysteine-lowering treatments may prevent one stroke in 143 people treated for 5.4 years. At this time, routine screening and treatment for hyperhomocysteinemia in stroke patients is not recommended unless there is clinical suspicion for homocystinuria.[3]

CARDIAC DISEASE AND STROKE

Cardiogenic thromboemboli are a common source of ischemic stroke. Thrombi may originate from the chambers of the heart, the cardiac valves, or from systemic veins gaining access to the arterial system through a right-to-left shunt in the heart (e.g., a patent foramen ovale (PFO) or atrial septal defect). The latter, termed *paradoxical embolism,* is still referred to as a cause of cardiogenic stroke though this may be a misnomer since the embolus comes from a noncardiac source, accessing the cerebral circulation via a structural heart defect. Paradoxical emboli can also occur in the setting of noncardiac shunts such as a large arteriovenous malformation (AVM) located elsewhere in the body.

Atrial Fibrillation/Atrial Flutter

Atrial fibrillation (AF) and atrial flutter combined are the most frequently associated conditions with cardiogenic stroke. Traditionally, AF was thought to lead to intracardiac clot formation from dysrhythmic contractility leading to stasis and subsequent thrombus formation in the left atrium or atrial appendage. However, given the dependence on comorbid vascular risk factors and advanced age to substantiate a high stroke risk in AF, this mechanism is probably not entirely explanatory.

In elderly patients with vascular risk factors, AF leads to structural remodeling of the left atrium. Whether AF is directly causal to stroke or whether stroke results from an atrial cardiopathy remains a matter of debate. Nevertheless, the discovery of persistent or episodic atrial fibrillation in patients with cardiogenic stroke is important as these patients benefit from anticoagulation more than antiplatelet therapy in the secondary prevention of stroke; long-term rhythm monitoring for the detection of atrial fibrillation is recommended following embolic stroke. The benefit of anticoagulation in patients without known atrial fibrillation but with atrial cardiopathy is not yet known.

Valvular atrial fibrillation, commonly from mitral valve stenosis, is also associated with an increased risk of stroke. Anticoagulation with warfarin is recommended for stroke prevention in patients with valvular AF, whereas direct oral anticoagulants have emerged as a preferred therapy for nonvalvular AF. See Chapter 5 for further discussion.

Patent Foramen Ovale

A PFO occurs when the foramen ovale fails to close after birth. This is a common cardiac finding, estimated to occur in one out of every four individuals and generally thought to be of no consequence in otherwise healthy people. However, young patients with embolic-appearing stroke tend to have a higher proportion of PFO, raising the question of causality in certain patients with stroke. Previously, surgical closure of PFO for secondary stroke prevention was not known to be of benefit but recent studies have suggested a long-term benefit for closure in select young patients with high-risk PFO and cryptogenic embolic stroke.

WOMEN'S HEALTH AND STROKE

In the United States, women are disproportionally impacted by stroke. Women experience a higher life-time risk of stroke, and as a result of stroke, women are more likely to be institutionalized and

TABLE 11-1 ■ Stroke Risk Factors Related to Sex

Risk Factor	Sex-Specific Risk Factor	General Risk Factor Stronger *or* More Prevalent in Women
Pregnancy	X	
Pre-eclampsia	X	
Gestational diabetes	X	
Oral contraceptive use	X	
Postmenopausal hormone replacement therapy	X	
Menopause	X	
Migraine with aura	X	
Atrial fibrillation		X
Diabetes mellitus		X
Hypertension		X
Depression		X
Psychosocial stress		X

Adapted from Bushnell C, Mccullough LD, Furie KL, et al: Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the american heart association/american stroke association. Stroke 45:5, 2014.[4]

have poorer outcomes including a higher mortality rate. Some of these sex-specific differences may be due to longer life expectancies in women and their older age at stroke onset, but certain vascular risk factors have higher prevalence or risk attribution in women including hypertension, diabetes mellitus, migraine with aura, and atrial fibrillation.[4]

There are also sex-specific stroke risk factors unique to women including pregnancy, pre-eclampsia, gestational diabetes, menopause, and exposure to exogenous hormones from oral contraceptives and hormone replacement therapy (Table 11-1). Because women tend to be underrepresented in major stroke trials, increasing inclusion and awareness in order to understand the unique aspects of stroke in women is critical.

Stroke in Pregnancy

Stroke in pregnancy is a major cause of long-term morbidity and an important cause of mortality for these women. Recent pooled estimates suggest that stroke may complicate as many as 30 out of 100,000 pregnancies, which is a threefold higher risk compared to young adults overall.[5] Stroke in pregnant women includes ischemic, hemorrhagic, and cerebral venous sinus thrombosis occurring in roughly equal proportions, which diverges from the general population where stroke incidence is predominantly ischemic.

The peripartum and postpartum periods tend to be the highest risk periods for stroke, with pregnancy-related hypertension and the acquired thrombophilia of pregnancy factoring most prominently (see Chapter 31). Other conditions that predispose to stroke can also manifest during pregnancy such as vascular dissection, congenital cardiac complications, moyamoya disease, and hemorrhage from aneurysm or vascular malformation.

Changes in the coagulation system that accompany pregnancy tend to manifest in the third trimester and are implicated in the increased risk of ischemic stroke and cerebral venous sinus thrombosis during pregnancy. These changes include a general increase in procoagulant factors (e.g., I, VII, VIII, IX, X, XII, XIII, and functional APC resistance), and a decrease in anticoagulants (e.g., antithrombin III and protein S).

Pre-eclampsia manifests in the latter half of pregnancy and is common among pregnant women with ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage. The mechanism of stroke related to pre-eclampsia and eclampsia is likely complex related to both abnormal vascular tone and prothrombotic effects. Pregnancy cardiomyopathy and amniotic fluid embolization are other causes of ischemic stroke in pregnancy.

Successful use of tissue plasminogen activator (tPA) as a treatment for acute ischemic stroke in pregnant women is understood at the case report level, and has not been studied empirically. Since tPA does not cross the placenta, it would not be expected to cause direct harm to the fetus; however, the major concern is the risk of placental hemorrhage and abruption prompting preterm delivery. Based on these limited case reports, tPA should be considered in the treatment of disabling ischemic strokes in pregnant women. For large-vessel occlusions, thrombectomy without intravenous thrombolysis is also a reasonable approach.

Women who experience stroke related to pregnancy may also have a higher risk of lifetime recurrent stroke. This may be due to a persistence of vascular risk factors that were simply unmasked in pregnancy (e.g., women with gestational diabetes have a higher risk of developing diabetes mellitus later in life). Women with stroke related to pregnancy should therefore be monitored closely to ensure proper lifetime risk reduction and optimal prenatal planning for future pregnancies.

Menopause

The physiologic transition into menopause is associated with an increased risk of ischemic stroke, and the preponderance of current data suggests that earlier menopause may be associated with a greater risk of stroke compared to those with typical age of onset.[4] Endogenous estrogen in the premenopausal state has been hypothesized as providing a protective effect against stroke risk; however, as reviewed in the section below, exogenous hormone replacement is now thought to increase the risk of stroke. Thus, hormone replacement therapy should be used cautiously in women with vascular risk factors, and only with the intent to control symptoms related to menopause.

Postmenopausal women experience an increase in all subtypes of ischemic stroke. While premenopausal women tend to have lower rates of hypertension when compared to their age-matched male counterparts, this reverses in postmenopausal women; hypertension tends to be more common in women with stroke than men with stroke, and women are also less likely to achieve adequate blood pressure control pre- and post-stroke. Whether there is a physiologic basis for medication resistance or higher rates of nonadherence is unknown. There is an increased incidence of comorbid vascular risk factors in elderly women including central obesity and elevated total cholesterol and LDL.

HEMATOLOGIC DISORDERS

While many conditions that predispose to stroke are broadly prothrombotic, there are a variety of major hematologic disorders that result in pathologic activation of hemostatic pathways and the coagulation cascade. These can arise from inherited, acquired, or mixed causes. Procoagulant perturbations of the coagulation cascade result from loss of function of a natural anticoagulant, such as protein C, protein S, or antithrombin III inherited or acquired deficiencies, or a gain of function of a procoagulant such as factor V Leiden, activated protein C (APC) resistance, or prothrombin gene mutations. Other conditions can bolster the hemostatic pathway including the antiphospholipid antibody syndrome, heparin-induced thrombocytopenia (HIT), and certain malignancies and their treatments (see below).

TABLE 11-2 ■ Components of Thrombophilia Screening

Basic coagulation screen: INR, aPTT
Antithrombin III functional assay
Protein C functional assay
Protein S functional assay
APC resistance assay, including genetic testing for factor V Leiden if APC abnormal
Prothrombin (factor II) gene mutation 20210A genetic testing
Antiphospholipid antibodies: anticardiolipin IgG and IgM, β2-glycoprotein-1 IgG and IgM, lupus anticoagulant assay

INR, international normalized ratio; aPTT, activated partial thromboplastin time; APC, activated protein C.

Current clinical guidelines from the American Heart Association and American Stroke Association do not specify for whom testing for hypercoagulable states should be performed post-stroke and this continues to be an area of variability in practice. The yield of thrombophilia testing is probably greatest in young patients with a cryptogenic stroke, or those with a personal or family history of thrombosis or unexplained pregnancy loss. See Table 11-2 for a suggested work-up for thrombophilia.

Antiphospholipid Antibody Syndrome

Antiphospholipid antibodies, a misnomer given their indirect action on anionic phospholipids, function in various ways to enhance hemostasis through their interaction with vascular endothelial cells and subsequent activation of the coagulation cascade. Antiphospholipid syndrome (APS) is defined by a venous or arterial thrombosis or pregnancy loss in the presence of persistent positivity of one or more antiphospholipid antibodies (aPL). APS can be a primary disorder or secondary to a rheumatologic condition such as systemic lupus erythematosus (SLE). The mechanism of stroke in APS may be a result of in situ arterial thrombosis or cardioembolism secondary to APS-related nonbacterial endocarditis (Fig. 11-1).

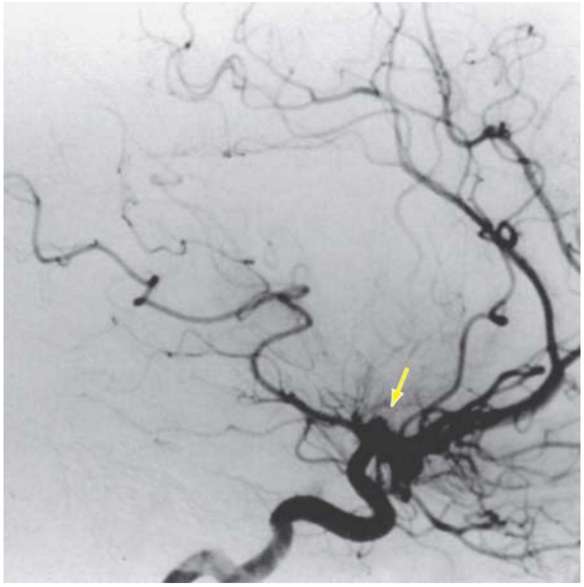

FIGURE 11-1 ■ Angiogram showing a middle cerebral artery occlusion (*arrow*) in a young woman with anticardiolipin antibodies, the lupus anticoagulant, and myxomatous mitral valve thickening. (From Coull BM, Levine SR, Brey RL: The role of antiphospholipid antibodies in stroke. Neurol Clin 10:130, 1992, with permission.)

Antiphospholipid antibodies that fulfill diagnostic criteria for APS include anti-β2 glycoprotein-I antibodies (aβ2GPI), anticardiolipin antibodies (aCL), or a positive functional lupus anticoagulant (LA) assay. There is emerging evidence that other antiphospholipid antibodies may be relevant to APS and stroke, although they are not yet formally part of the diagnostic criteria. These other antibodies include antiphosphatidylserine (aPS), antiphosphatidylserine-prothrombin antibodies (aPS/PT), antiannexin A5, and antiphosphatidylethanolamine (aPE).[6] In terms of serologic risk prediction, the highest risk is often attributed to (1) triple positivity (aβ2GPI, aCL, and LA), (2) moderate to high titers, and (3) IgG isotype (versus IgM). The strongest association with noncriteria antibodies and risk of stroke and death is with aPS/PT.

There are currently no disease-modifying drugs used in the management of APS, and the mainstay of therapy consists of antithrombotic medications to reduce the risk of future thrombotic events. The data regarding an optimal regimen do not address the safety and efficacy of newer oral anticoagulants for APS. Current expert consensus is that standard intensity warfarin (INR 2–3) should be used for secondary stroke prevention in APS unless there are significant bleeding concerns or a perceived low risk of recurrent thromboembolic events.[3] If warfarin is not initiated for any reason, patients should be treated with antiplatelet therapy for secondary prevention. Patients with stroke and aPL who do not meet criteria for APS are not recommended for treatment with anticoagulation for secondary stroke prevention.

Given the increasing awareness that aPL may be an independent risk factor for thromboembolism, primary stroke prevention is an important clinical question with insufficient data. At this time, many consider antiplatelet therapy in asymptomatic aPL carriers if there are co-morbid vascular risk factors; however it is unknown whether this exerts a significant stroke risk reduction in otherwise healthy, young patients.

Sneddon Syndrome

Sneddon syndrome is a neurocutaneous disorder associated with antiphospholipid antibodies that primarily affects middle-aged women. Histopathologically, Sneddon syndrome is a noninflammatory thrombotic arteriopathy of medium and small vessels in the dermis and in the brain. Skin biopsy reveals dermal inflammation without vasculitis. Clinically, it is characterized by recurrent strokes and livedo reticularis. Affected patients may also have Raynaud phenomenon or acrocyanosis of the digits. Antiphospholipid antibodies are often prominent and progressive cognitive decline from the arteriopathy may occur even in young persons. Accordingly, any young patient presenting with progressive cerebrovascular disease or cognitive decline and livedo reticularis should be evaluated for the presence of antiphospholipid antibodies. Optimal treatment is unknown and both antiplatelets and anticoagulants have been used. Immunosuppressive therapy is not routinely indicated.

Factor Deficiencies

Antithrombin III, protein C, and protein S are natural anticoagulants that regulate the coagulation cascade (Fig. 11-2). While these genetic deficiencies are more strongly implicated in the pathogenesis of venous thromboembolism, they underlie a small proportion of arterial stroke, notwithstanding the presence of a venous–arterial conduit such as a PFO. They factor more prominently in the pathogenesis of ischemic stroke in children and young

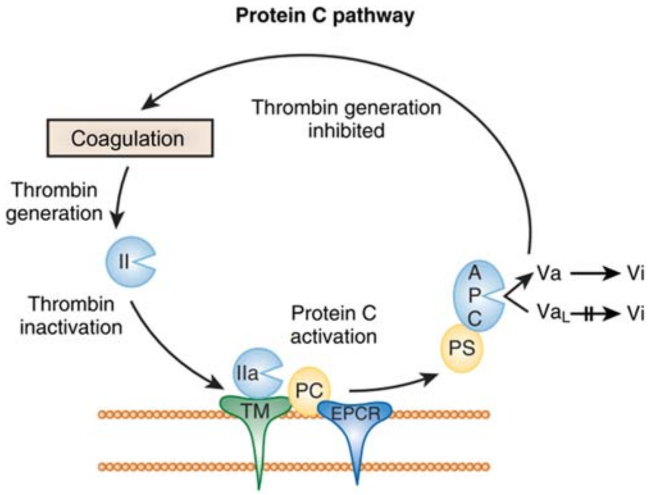

FIGURE 11-2 ■ Protein C pathway. Activation of coagulation triggers thrombin (IIa) generation. Excess thrombin binds to thrombomodulin (TM) on the endothelial cell surface. Once bound, the substrate specificity of thrombin is altered so that it no longer acts as a procoagulant but becomes a potent activator of protein C (PC). Endothelial protein C receptor (EPCR) binds PC and presents it to thrombomodulin-bound thrombin, where it is activated. Activated protein C (APC), together with its cofactor, protein S (PS), binds to the activated platelet surface and proteolytically degrades factor Va (Va) into inactive fragments (Vi). Because factor Va is a critical component of the prothrombinase complex, factor Va inactivation by APC attenuates thrombin generation. Because factor $\text{Va}_{\text{Leiden}}$ (FVa_{L}) is resistant to inactivation by APC, patients with the factor V_{Leiden} mutation have reduced capacity to regulate thrombin generation. (From Anderson JA, Weitz JI: Hypercoagulability and uncommon vascular diseases. In Jaff MR, White CJ (eds): Vascular Disease: Diagnostic and Therapeutic Approaches. Cardiotext Publishing, 2011. Used with permission from Cardiotext Publishing.)

adults, and their significance in older adults is less clear.

Inherited deficiencies occur in an autosomal dominant fashion, thus family history may be revealing. Acquired deficiencies may be due to conditions that decrease synthesis, increase consumption, or facilitate clearance. Common sources of acquired deficiencies include liver disease, treatment with L-asparaginase therapy, therapy with vitamin K antagonists, sepsis, disseminated intravascular coagulation (DIC), and acute thrombosis, including stroke. Any abnormal result in the setting of an acute stroke should be repeated at a later date to assure the result is not a false positive in the setting of an acute thrombosis. Acquired antithrombin III deficiency has also been described in polytrauma, malignancy, burns, extracorporeal circulation, concurrent hormone replacement therapy or oral contraceptive use, preeclampsia, and pregnancy-induced hypertensive illness.[7] Antithrombin III and protein S deficiencies can be secondary to nephrotic syndrome. Functional assays are the preferred method for screening for these disorders since deficiencies may be quantitative or qualitative. Any abnormality detected on initial screening should be repeated at an interval to ensure validity.

There is a lack of prospective studies guiding therapy for secondary stroke prevention in the setting of these thrombophilias. Antithrombin III deficiency has the highest risk for recurrence of thrombotic events. Options for treatment range from lifelong anticoagulation for secondary prevention to anticoagulation only during high-risk periods. Counseling is important as any patient with an inherited deficiency should be advised of the risks of thrombosis with oral contraceptive use, prolonged bed rest, the post-operative state, and pregnancy.

Inherited Thrombophilias

Certain inherited thrombophilias result from gain-of-function mutations whose cumulative effects are procoagulant. Factor V Leiden refers to a single-point mutation on factor V that renders the protein resistant to neutralization by APC. Factor V Leiden is a primary cause of APC resistance but acquired APC resistance can also occur as a result of pregnancy, oral contraceptives, and hormonal replacement therapy. Both factor V Leiden heterozygosity and homozygosity confer an increased risk of venous thromboembolism; however, the association with arterial stroke independent of a PFO is debated.

The prothrombin (or factor II) G20210A gene mutation leads to an increased production of prothrombin, which results in a procoagulant state either by enhancing thrombin generation or inhibiting factor Va inactivation by APC, resulting in increased risk of venous thromboembolism. Similar to factor V Leiden, there is an association with arterial stroke in young patients; however the contribution of a PFO has not been consistently addressed in studies.[8]

The decision to treat with antiplatelet or anticoagulation for secondary stroke prevention due to these gene mutations is made on an individual basis. In those who have recurrent stroke in the setting of these abnormalities, anticoagulation should be considered.[3]

Sickle Cell Anemia

In addition to a host of peripheral complications, sickle cell anemia is a strong risk factor for ischemic stroke in children and adults. Incidence is highest in children, with most strokes occurring in the first decade of life. Silent infarcts are common in patients with sickle cell disease as well. Hemorrhagic strokes and cerebral venous sinus thromboses are less common manifestations of sickle cell anemia.

The mechanism of stroke in sickle cell anemia was believed to be analogous to the peripheral complications of sickle cell formation during sickle cell crises involving insoluble deoxygenated hemoglobin aggregates within vessels that form local thromboses during crises. However, the current consensus is that stroke in sickle cell anemia stems from an acquired vasculopathy secondary to accumulated endothelial damage in large- and medium-sized vessels. Vessel imaging shows characteristic segmental stenosis in the internal carotid and proximal portions of vessels in the circle of Willis. These stenoses can evolve into a moyamoya-like vasculopathy featuring progressive narrowing and resulting in the development of arcades of collateral vessels. The locations of vessel stenoses are thought to be the primary sites of thrombosis leading to ischemic stroke and the pattern of ischemic stroke on imaging is typically a combination of watershed and thromboembolism.

Transcranial Doppler (TCD) ultrasonography is a useful screening tool to monitor pediatric patients with sickle cell anemia for vasculopathy by way of measuring flow velocity at regular intervals. Studies have shown that the risk of stroke could be reduced from 10 percent per year to less than 1 percent per year with routine exchange transfusion therapy guided by TCD velocities. Subsequent trials investigated the effect of stopping exchange transfusions once TCD velocities had normalized and were ended prematurely because about one-third of patients who had stopped monthly exchange transfusions redeveloped high-risk velocities. Based on these data, it appears that exchange transfusions may be required indefinitely, although such an extensive treatment regimen should be weighed against the risks of iron overload, transfusion reactions, and donor-borne transmission of infectious diseases. Guidelines on primary prevention of ischemic stroke from the American Heart Association and the American Stroke Association recommend that children with sickle cell disease be screened with TCD beginning at 2 years of age.

Cryoglobulinemia

Cryoglobulins are serum immunoglobulins with abnormal thermal solubility which precipitate below 37°C in vitro. They can be monoclonal and driven by a primary B-cell malignancy or monoclonal gammopathy or they can be polyclonal and driven by persistent lymphoproliferation in the setting of an autoimmune disorder or chronic infection. The autoimmune diseases associated with cryoglobulins include SLE, Sjogren syndrome, and rheumatoid arthritis. Infections commonly associated with cryoglobulins include hepatitis C and B, human immunodeficiency virus (HIV), and other bacterial or parasitic infections.

Cryoglobulins may be asymptomatic, but cryoglobulinemia manifests with certain core features including cutaneous vasculitis, arthralgias, peripheral neuropathy, and glomerulonephritis. Stroke and other central nervous system (CNS) manifestations are a less commonly recognized presentation of cryoglobulinemia, usually in association with hepatitis C infection. The mechanism of stroke in cryoglobulinemia is speculative but may result from cryoprecipitation, defective clotting and platelet functions, immune complex-mediated vasculitis and intravascular hemolysis, or progressive vasculopathy.

Plasmapheresis has been effective in some patients with neurologic complications, presumably through lowering of cryoglobulinemia and therefore improvement of the microcirculation. Beneficial results may be obtained in some cases by minimizing cold exposure. Immunosuppressive agents have been used in noninfectious cryoglobulinemia, but controlled clinical trials are lacking and current treatment regimens are based on expert opinion.

INFECTIONS

Acute systemic infections have been linked to an increased risk of ischemic stroke, highlighting some of the speculation underlying the seasonal variation of stroke incidence, which is higher in winter months. Stimulation of inflammatory cascades with systemic infection is thought to promote atherosclerotic plaque formation and rupture as well as thrombosis.

Bacterial endocarditis is an important mechanism of stroke in the setting of systemic infection wherein septic debris embolize to the brain and lead to ischemia, microhemorrhages, and mycotic aneurysms due to degradation of the vessel wall from pathogen infiltration (see Chapter 6). Given the proclivity for vessel wall fragility and hemorrhage, intravenous thrombolysis for acute stroke is contraindicated in the setting of known bacterial endocarditis.

Stroke may complicate certain CNS infections as well. Stroke may be due to an infectious vasculitis wherein pathogenic invasion of blood vessels leads to segmental vessel narrowing, thrombosis, or both. A parainfectious vasculitis, one mediated by the inflammatory response itself, may also underlie stroke in CNS infections. While some infections are readily apparent such as acute bacterial meningitis, others present with nonspecific features and may go undiagnosed. Particularly in young patients without traditional stroke risk factors or in those who are immunocompromised, stroke evaluation should include a thorough evaluation for infection including systemic and cerebrospinal fluid (CSF) evaluations. Table 11-3 summarizes the common mechanisms and infectious triggers of stroke.

	Infectious causes
Preceding or concomitant systemic infection, outside the CNS	Influenza *Chlamydia pneumoniae* *Helicobacter pylori* *Porphyromonas gingivalis*
Preceding or concomitant infection, contiguous with the CNS	*Streptococcus pneumoniae* sinusitis *Haemophilus influenzae* sinusitis *Moraxella catarrhalis* sinusitis *Aspergillus fumigatus* sinusitis Mucormycosis sinusitis
Total non-specific infectious burden	More than one current or previous systemic infection
Vasculitis and mycotic aneurysm	HIV Varicella zoster virus Syphilis Neuroborreliosis Epstein-Barr virus Cytomegalovirus Tuberculosis Neurobrucellosis
Vascular remodeling	HIV Syphilis
Promotion of a hypercoagulable state	Hepatitis C
Infectious endocarditis	*Staphylococcus aureus* Coagulase-negative staphylococci Viridians group streptococci *Streptococcus bovis* Enterococci HACEK bacteria *Escherichia coli* *Klebsiella pneumoniae*
Cardiogenic emboli to the cerebral vasculature from dilated cardiomyopathy	Chagas disease

HACEK=*Haemophilus parainfluenzae, Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominus, Eickenella corrodens,* and *Kingella kingii.*

TABLE 11.3 Mechanism of infectious caused and triggers of stroke

Reprinted with permission from Fugate JE, Lyons JL, Thakur KT, et al: Infectious causes of stroke. Lancet Infect Dis 14:869–880, 2014.

Acute Bacterial Meningitis

Ischemic strokes are relatively common and highly morbid complications of pyogenic bacterial meningitides (see Chapter 38 for a further discussion of acute bacterial meningitis and Chapter 47 for a discussion of chronic meningitis). The presentation of stroke in the context of a bacterial meningitis may be indistinguishable from other complications such as cerebritis, abscess, and seizure, and therefore ancillary testing with imaging is critical to diagnose stroke in this setting.

The timing of stroke related to bacterial meningitis is typically within days to weeks of the infection and often occurs despite appropriate antimicrobial therapy and sterilization of the CSF. Strokes make be due to a large- and medium-vessel vasculopathy as many of these vessels are located at the base of the brain in close proximity to subarachnoid exudates. Many patients therefore present with large-territory ischemic lesions or those in a watershed pattern. Small-vessel thrombotic strokes may occur as well. A chronic vasculopathy resembling moyamoya syndrome has also been described and may increase the risk of delayed stroke. Beyond antimicrobial therapy and adjunctive corticosteroids, the optimal management of vascular complications related to bacterial meningitis is not known. There is no known benefit of antithrombotic medications or an extended course of corticosteroids in these circumstances.

Tuberculous Meningitis

Tuberculosis (TB) remains an international public health concern, and it affects both immunocompromised and competent patients (see Chapter 40). Tuberculous meningitis (TM) is the primary neurologic complication of TB and can occur during primary infection or in the latent stage due to reactivation of the dormant mycobacterium. TM is characteristically a subacute meningitis and may be complicated by ischemic stroke, intraparenchymal tuberculomas, or multiple cranial neuropathies due to compression from hydrocephalus. Intracerebral hemorrhage and aneurysm formation related to tuberculous meningitis are rare.

Ischemic stroke that complicates TM is characteristically localized to the "tuberculoid zone," which includes the caudate nucleus, anterior thalamus, and anterior limb of the internal capsule; this location's involvement is due to smaller perforator vessels affected by a TM-related infiltrative vasculitis which may be further stretched by concomitant hydrocephalus. Cortical and subcortical stroke may also occur from vasculitis of the larger intracranial arteries embedded in inflammatory exudate. A prothrombotic state may also contribute to stroke in TM.

The risk of ischemic stroke is thought to be related to the severity of meningitis at presentation.[10] In addition to antitubercular treatment, there may be a benefit of adjunctive steroids in reducing mortality and morbidity related to TM complicated by stroke. Aspirin has been considered as an adjunct for preventing stroke related to TB meningitis but there are little data to support its use.

Syphilis

Despite a downtrend in syphilis infections following the introduction of penicillin, the incidence of syphilis has been on the rise over the past two decades. Co-infection with HIV is also common and thus neurologic and neurovascular complications of these combined infections may be compounded (see Chapter 39).

The pathogenesis of syphilis is often referred to in stages, and the neurologic consequences of syphilis vary accordingly. *Treponema pallidum*, the pathogen responsible for syphilis, is known to enter the CNS during primary infection and may remain clinically silent in untreated patients. Meningitis and meningovascular syphilis manifest in the early stages (i.e., within months to several years) of the infection, while parenchymal disorders, dementia, and tabes dorsalis occur in the late stage (i.e., after 1–2 decades) of the infection.

Ischemic stroke is a consequence of the meningovascular form of syphilis, and frequently due to large and medium-sized vessel involvement. The presentation is frequently, but not always, preceded by a subacute encephalitic prodrome with symptoms including insidious headache, neck pain, or seizure.

The diagnosis of neurosyphilis is challenging. *T. pallidum* cannot be cultured in vitro, and the identification of infection is therefore dependent on serologic evaluation. Treponemal serum testing (i.e., fluorescent treponemal antibody absorption or syphilis enzyme immunoassay) is a useful screening tool for detecting antibodies to the bacterium; however these tests remain reactive indefinitely despite treatment. A negative test can therefore be useful in ruling out neurosyphilis, but a positive test will not distinguish current from a prior treated infection. Non-treponemal tests such as rapid plasma reagent (RPR) and venereal disease research laboratory (VDRL) are useful for diagnosing meningovascular syphilis since they are usually reactive in the early phase of the infection. Classic CSF findings include an elevated protein and lymphocytic pleocytosis.

Treatment of neurosyphilis including meningovascular syphilis consists of intravenous penicillin G. It is recommended to perform regular screening with repeat CSF testing every few months to ensure a resolution of pleocytosis and loss of reactivity of VDRL. Vascular changes may be permanent, and daily aspirin may be useful for secondary stroke prevention.[10]

SYSTEMIC LUPUS ERYTHEMATOSUS

Stroke is common in patients with SLE. Although most strokes in SLE are ischemic, intracerebral hemorrhage has been reported typically in the setting of concurrent thrombocytopenia. Ischemic stroke in SLE most commonly affects younger patients, although elderly patients with SLE also are at high risk likely due to the presence of other vascular risk factors that may act synergistically with SLE.

Antiphospholipid antibody syndrome can be seen secondary to SLE. The most frequent mechanisms for ischemic stroke in SLE are either cardiogenic embolus from nonbacterial thrombotic endocarditis (termed Libman–Sacks endocarditis in SLE) or an antibody-mediated hypercoagulable state. Both tend to be associated with antiphospholipid antibodies, and therefore laboratory testing for APS should be performed in any patient with SLE and an unexplained stroke.

The incidence of an inflammatory cerebral vasculitis in SLE is extremely low in autopsy studies, making this an unlikely cause of stroke in these patients. A noninflammatory vasculopathy secondary to vessel-wall hyalinization and endothelial proliferation has been described more frequently. The mechanism of SLE-related vasculopathy is unclear, although possible mechanisms include endothelial damage by antineuronal antibodies or immune complex deposition.

Anticoagulant therapy may reduce the risk of stroke recurrence in patients with SLE. Oral anticoagulation is warranted in patients with SLE who have concurrent risk factors of cardiac valvular lesions or APS. Outside of these indications, standard secondary prevention involves antiplatelet medications. Given the absence of inflammatory vascular lesions in patients with SLE who have strokes, corticosteroids probably have no role outside of their treatment for systemic inflammation.

ONCOLOGY AND STROKE

Ischemic and hemorrhagic strokes are common in patients with both solid and hematologic malignancies and present unique challenges in management. The unique mechanisms of stroke in this population include acquired coagulopathy leading to a thromboembolic state or in situ thromboses, nonbacterial endocarditis resulting in cardioembolic stroke, and direct tumoral invasion of vascular structures. The cause of cerebrovascular events in patients with cancer can vary with the type of primary tumor, extent of malignant dissemination, and the type of anticancer therapy administered.

Coagulopathy in the Setting of Cancer

Disorders of coagulation in cancer patients have been linked to many different malignancies but are most commonly described with adenocarcinomas, such as pancreas, lung, colon, breast, prostate, and gastric cancer, and leukemias. Although abnormalities of coagulation are seen quite commonly in patients with cancer, these coagulopathies are rarely symptomatic. When present, a coagulation disorder may manifest with superficial or deep venous thromboses, nonbacterial thrombotic endocarditis (NBTE), or migratory thrombophlebitis, all of which may lead to ischemic stroke. Malignancy-related coagulopathy can culminate in DIC and result in both ischemic and hemorrhagic complications, the latter due to the consumption of platelets and clotting factors. Patients with coagulopathy in the setting of malignancy tend to have a poor prognosis since this usually occurs in the setting of advanced and disseminated disease.

Nonbacterial Thrombotic Endocarditis

NBTE, also known as marantic endocarditis, is an important source of stroke in patients with cancer. The pathophysiology involves the deposition of sterile, friable fibrin on heart valves that may result in systemic embolization to the brain and other organs (Fig. 11-3).

The pathogenesis of NBTE in malignancies may emanate primarily from an underlying cardiac valvular abnormality that predisposes to the deposition of platelets and fibrin, facilitated by malignancy-related hypercoagulability. Once valvular damage occurs, underlying exposed collagen can act as a nidus for platelet adhesion and subsequent thrombus formation. Microscopically, the valvular lesions consist of agglutinated blood and platelet thrombi in the absence of an inflammatory reaction. Embolic fragments are primarily composed of fibrin.

Most vegetations are multiverrucous and less than 3 mm in size, which accounts for the relatively low

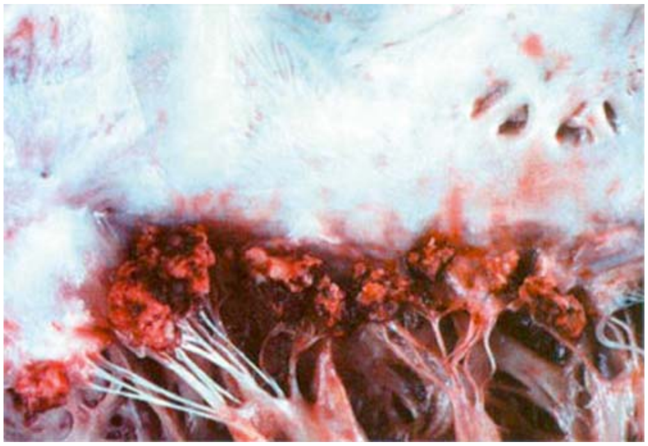

FIGURE 11-3 ■ A typical mitral valve lesion in a patient with lupus and nonbacterial thrombotic endocarditis (NBTE). (Photograph courtesy of Dr. William D. Edwards, Division of Anatomic Pathology, Mayo Clinic Rochester.)

diagnostic yield of conventional transthoracic echocardiography compared with transesophageal echocardiography. Diffusion-weighted MRI sequences of the brain may show multiple strokes of differing sizes in multiple vascular territories or border zone regions. Once a diagnosis of NBTE is made, treatment of the primary malignancy should be the primary focus. If there is no recognized malignancy, a thorough search should be undertaken for occult cancer as well as autoimmune and rheumatologic disorders that can share this appearance. Recent guidelines have recommended use of low-molecular-weight or unfractionated heparin for treatment of NBTE with evidence of emboli.

Stroke Related to Cancer Therapy

Stroke directly related to chemotherapy is a relatively rare occurrence. Platinum-containing compounds are most commonly implicated; the pathophysiology of this relationship is not entirely known, but may be a consequence of induced vasospasm, endothelial dysfunction, or other procoagulant changes.

The chemotherapeutic agent L-asparaginase is frequently associated with cerebral infarction, typically from cerebral venous sinus thrombosis. Most patients make a good clinical recovery. Although the cause of sinus thrombosis is unclear, L-asparaginase may lead to a decreased partial thromboplastin time (PTT) and increased platelet aggregation, as well as antithrombin III and plasminogen deficiencies.

Radiation-induced vasculopathy of the cervical and intracranial carotid arteries is an additional potential cause of stroke in patients treated for cancer. The interval from radiation treatment to onset of occlusive cerebrovascular disease ranges from month to decades. Angiography reveals occlusion or extensive stenosis of the arteries in the previous radiation field; carotid artery lesions in patients irradiated for head and neck cancers are the most common. Limited data on treatment options for symptomatic extracranial carotid disease in the setting of radiation damage are available, but carotid stenting is typically preferred over endarterectomy as surgical dissection can be challenging.

Intracerebral Hemorrhage

Intracerebral hemorrhage is most commonly reported with leukemic conditions, specifically acute promyelocytic leukemia. Although the pathogenesis of the hemorrhage has been postulated to involve infiltration and rupture of vessels by leukemic nodules or damage to small vessels from hyperviscosity, most patients with intracranial hemorrhage do not have evidence of leukostasis, leukemic nodules, or perivascular leukemic infiltration on histologic examination. Among the patients who do have evidence of leukemic infiltration, the peripheral white blood cell count is usually above $70,000/\text{mm}^3$. In addition to leukemic conditions, lymphoma and multiple myeloma may cause hemostatic deficiencies that predispose to brain hemorrhage through inhibition of fibrin formation by excess immunoglobulins.

Direct Tumor Effects

Direct tumor effects include intratumoral hemorrhage, arterial and venous invasion by tumor mass or leptomeningeal infiltrates, and tumor emboli. Tumor emboli occur rarely and exclusively in patients with solid tumors; they are virtually impossible to distinguish from thrombogenic emboli on clinical grounds alone. These metastatic emboli typically result from heart or lung tumors—atrial myxomas may shower small tumor fragments into the vasculature and lung tumor embolism may occur at the time of thoracotomy. Tumors that demonstrate aggressive intravascular invasion such as choriocarcinoma may also cause cerebrovascular events. Neoplastic aneurysms, with subsequent rupture causing hemorrhage, have been described; tumor emboli may invade an arterial wall after acute occlusion of the vessel, eventually resulting in dilatation and aneurysm formation. Cerebral venous sinus thrombosis may occur by direct tumor invasion from neuroblastoma, lung carcinoma, and lymphoma.

MIGRAINE AND STROKE

Migraine is a highly prevalent and costly disorder affecting both children and adults. While often thought of as a pure headache syndrome, it is a major cause of disability worldwide.

There is a strong relationship between stroke and migraine. The most frequent association between the two entities is the clinical overlap of their two presentations. The cortical-spreading depolarization that is the pathophysiologic underpinning of a migraine aura causes symptoms that may be indistinguishable from cerebral ischemia including aphasia, hemibody sensorimotor phenomena, and a myriad of vision changes.

Migraineurs, specifically those with the migraine with aura subtype, have an independently increased risk for stroke and other cardiovascular disorders including coronary artery disease, peripheral vascular disease, and retinal vascular disorders. Migraine patients also have a higher frequency of silent white matter abnormalities on MRI. The association between migraine and hemorrhagic stroke is less well-established.

The mechanism linking migraine and stroke is largely speculative, but hypotheses relate to intrinsic endothelial dysfunction in migraineurs, neurogenic inflammation from prolonged cortical-spreading depolarization, hypercoagulability with microemboli formation and right-to-left shunting, and the potential vasoconstrictive effects of migraine medications.[11]

Evidence for overlapping pathophysiology is best typified by the rare occurrence of a *migrainous stroke*. Migrainous strokes present initially as a migraine with an aura typical of the individual's previous attacks; however, the aura persists, and subsequent neuroimaging demonstrates an acute stroke in a causal vascular territory.

Stroke Prevention in Migraine

Given the rarity of migrainous stroke and lack of understanding of the migraine–stroke overlap, it is not recommended to use migraine-specific medications (preventative or abortive) as a stroke reduction strategy. The question of whether migraine medications ameliorate the future risk of stroke is unknown and there is no evidence to support a stroke-protective effect. Minimizing concomitant stroke risk factors in migraineurs such as hypertension, smoking, or high-estrogen-content oral contraceptives should be stressed. Although there is some theoretical basis to suggest microemboli mediated by PFO contribute to stroke and migraine independently, there is no evidence supporting PFO closure as a treatment for migraine. The use of triptans and ergot derivatives for migraine and their risk of stroke are discussed in the section below.

DRUGS AND STROKES

Estrogens

Estrogens have been shown to increase serum levels of several coagulation cascade proteins, including fibrinogen, factors II, VII, IX, X, and XII, and protein C. Exogenous use of estrogen in contraceptive formulations and postmenopausal hormonal replacement is associated with an increased risk of ischemic stroke. The risk of estrogens in gender-affirming hormone supplementation for transwomen is largely unmeasured but has been extrapolated from nontransgender individuals.

The belief in a protective effect of estrogen against stroke originates from the view that the increase in incidence of stroke and cardiovascular disease in postmenopausal women parallels the decline in endogenous estrogen. Research from the Women's Health Initiative and others found, in fact, that hormone replacement therapy with estrogen is actually associated with an increased risk of stroke.[12] This risk of stroke does not appear to be modifiable with respect to a woman's age upon initiation of therapy, temporal proximity to menopause, or whether formulations contain opposing hormones.

The association between oral contraceptive pill (OCP) use and stroke has been known for decades. Early studies demonstrated a much higher risk of stroke associated with estrogen-containing pills, which has been attributed to the higher dose of estrogen in earlier formulations. When OCPs were first available in the 1960s, the estrogen dose was approximately 150 μg compared to 20 to 50 μg in current formulations. The current risk of stroke associated with modern, estrogen-containing OCPs is overall small, but certain conditions appear to elevate the associated risk including comorbid hypertension, tobacco use, a history of migraine with aura, and factor V Leiden mutation or other inherited thrombophilias. Alternatives to estrogen-containing OCPs should be considered in women with other vascular risk factors. It is recommended to screen for other underlying thrombophilias (e.g., protein C and protein S deficiency, antithrombin III deficiency, the factor V Leiden mutation) in women who have a stroke while taking oral contraceptives, since contraceptive use may simply unmask previously latent clotting abnormalities.

Anabolic Androgenic Steroids

Anabolic androgenic steroids are used in the treatment of hypogonadism. Abuse of anabolic steroids is most often associated with performance enhancement in athletes, and dosages can far exceed those used for therapeutic purposes. The relatively low levels of testosterone used in therapeutic supplementation have not been definitively linked with an increased risk of stroke, but elevated testosterone levels in the setting of androgenic steroid abuse do seem to increase the risk of atherothrombotic events including ischemic stroke and venous thromboembolism, as well as cerebral venous sinus thrombosis.[13] The effect of high doses of testosterone on unfavorable lipid profiles, platelet aggregation, production of procoagulant factors, erythrocyte overproduction, and hypertrophic cardiomyopathy serve a theoretical basis for the pathophysiologic mechanism that may underlie the association.

Alcohol

Alcohol has long been recognized for its broad range of effects on the CNS. Heavy alcohol use is linked to an increased risk of ischemic, hemorrhagic strokes, and subarachnoid hemorrhage. Low to moderate alcohol use may be associated with a decreased risk of ischemic stroke compared to no alcohol use (Fig. 11-4), although the causality of this association has been questioned and will require further exploration. This potentially protective association with low to moderate alcohol use is not seen in relation to intraparenchymal or subarachnoid hemorrhage.

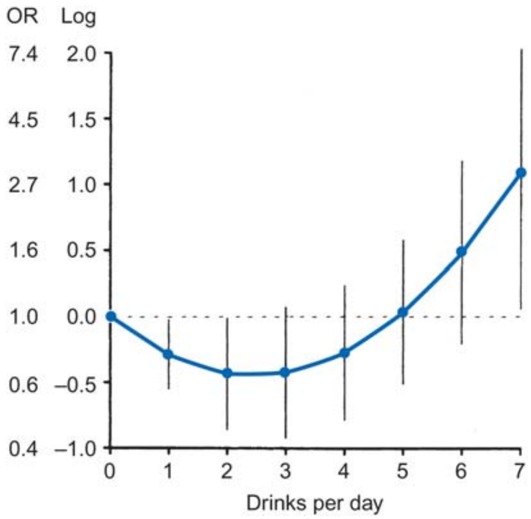

FIGURE 11-4 ■ Relationship between alcohol and the risk of ischemic stroke. OR denotes odds ratio for ischemic stroke. (From Sacco RL, Elkind M, Boden-Albala B, et al: The protective effect of moderate alcohol consumption on ischemic stroke. JAMA 281:57, 1999, with permission. © 1999, American Medical Association.)

Several pathophysiologic relationships may exist between alcohol and stroke. Alcohol may induce atrial fibrillation, alcoholic cardiomyopathy, and global cardiac akinesis, thereby predisposing to cardioembolism. Alcohol has also been linked to hypertension, increased platelet aggregation, abnormal activity of the clotting cascade, and reduced fibrinogen levels. Alcohol consumption contributes to systolic hypertension along with a decrease in the production of circulating clotting factors by the liver, both of which may contribute to the development of hemorrhagic stroke.

Tobacco

Tobacco use remains a leading preventable cause of stroke and death worldwide. Although the reduction in tobacco smoking in the United States represents a major public health accomplishment, the percentage of Americans who smoke remains high. Second-hand smoke exposure, including among children, remains a continued risk factor for stroke. Tobacco use in the form of E-cigarettes has also become highly popular particularly in young adults and adolescents.

The effects of tobacco smoking lead to chronic inflammation, insulin resistance, proatherogenic lipid profiles, and endothelial injury from oxidizing chemicals and nicotine. These chemicals promote atherosclerotic plaque formation in coronary and peripheral arteries.[14] The multisystemic effects of tobacco smoking are now well-known and include cardiovascular and cerebrovascular disease, respiratory conditions, and cancer. Importantly, smokers who abstain from smoking seem to eventually resume a lifetime risk of stroke similar to that of nonsmokers.

Amphetamines

Amphetamines and amphetamine derivatives constitute a class of drugs used for weight loss and as stimulants. The route of administration can be intravenous, oral, intranasal, or inhaled. The estimated prevalence of amphetamine abuse worldwide is nearly double that of cocaine.[13] Amphetamines are synthetic sympathomimetics that have been causally linked to ischemic and hemorrhagic strokes through a variety of mechanisms including cardiac arrhythmia with cardioembolism, cerebral vasculitis, vasoconstriction, and acute hypertension. Amphetamines may also lead to aneurysm formation and rupture due to frequent bouts of acute hypertension.

Cocaine

Cocaine is a synthetic sympathomimetic that is associated with an increased risk of stroke in users regardless of the route of exposure. Ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhages have been described in association with acute cocaine use, but long-term users may also experience accelerated vascular disease which causes stroke through more traditional intermediate phenotypes (e.g., large-vessel atherosclerosis). Arterial dissection has also been described.

Cannabis and Cannabinoids

Cannabis is the most widely used psychoactive substance in the world and has now been made legal in several countries around the world for therapeutic and recreational use. An increased risk of ischemic stroke associated with cannabis has been reported, and mechanisms include cerebral vasospasm and the prothrombotic effect of tetrahydrocannabinol (THC) on platelet aggregation. Synthetic cannabinoids represent a growing public health concern because of numerous safety issues and availability for legal purchase; this class of drugs contains highly active metabolites with a higher potency compared to THC. Case reports have highlighted an association with ischemic stroke, severe cardiac events, cerebral vasospasm, and hemorrhagic stroke. Since synthetic cannabinoids are not detected in routine toxicology, complete epidemiologic data are lacking.

Migraine Medications

Triptans and ergot alkaloid derivatives are two major classes of migraine abortive therapy with vasoconstrictive effects that have been linked with stroke. Because of the long-recognized association between migraine and ischemic stroke, a causal relationship has not been confirmed. In patients with a history of cardiovascular or cerebrovascular disease, triptans and ergot alkaloids are not relatively contraindicated.

GENETICS OF STROKE

Stroke remains a leading cause of death and permanent disability in the United States and worldwide. Primary and secondary stroke prevention strategies make up a limited armamentarium that is often bluntly applied. The application of genomic studies that would allow for individualized stroke risk prediction and novel drug development will have substantial implications in stroke prevention and public health.

Most strokes are a result of multiple intersecting genetic pathways and environmental exposures. The heritability of stroke calculated from genome-wide association studies (GWAS) is estimated at 30 to 40 percent.[15] To date, various GWAS have identified at least 35 variants (mainly single nucleotide polymorphisms) with links to stroke. Risk loci have been identified for all major ischemic stroke subtypes and hemorrhagic stroke.[15] Most of these loci have a minor allele frequency in the population and individually attribute only modest increases in stroke risk. Many are in nonprotein-coding DNA. Some of these genetic variants may be mediated by known stroke risk factors such as hypertension, but a substantial portion are not yet confirmed to be related to any known stroke pathway. The association of some variants exclusively with one stroke subtype suggests the possibility of novel pathophysiologic discovery in the future.

Although the majority of sporadic strokes arise through complex genetics and exposures, a small minority of strokes are caused by single-gene mutations with Mendelian inheritance. In some of these conditions, stroke is the defining complication and systemic symptoms are not appreciated. These conditions include the heritable small-vessel diseases CADASIL (i.e., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; *Notch 3*), CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; *HTRA1*), and PADMAL (pontine autosomal dominant microangiopathy with leukoencephalopathy; *COL4A1*). Among these, CADASIL is the most common hereditary stroke disorder.

However, there are several monogenetic diseases that are predominantly characterized by their systemic manifestations but also increase the risk for ischemic stroke. These include: sickle cell disease (*HBB*), a common cause of stroke in children; Fabry disease (*GLA*), discussed later; Marfan syndrome (*FBN1*), in which there may be skeletal, cardiac, aortic, and ocular abnormalities; and Ehlers–Danlos type IV, vascular subtype (*COL3A1*), in which there are characteristic facial features (acrogeria), thin translucent skin, easy bruising, and arterial, intestinal and uterine complications. Other such disorders include hereditary hemorrhagic telangiectasia (*ENG*, *ALK1*, others), with arteriovenous malformations that lead to bleeding in the lungs, central nervous system, and liver; homocystinuria (*CBS*, *MTHFR*, others), leading to vascular disease, cognitive and developmental disability, musculoskeletal abnormalities, and ocular manifestations; pseudoxanthoma elasticum (*ABCC6*) causing retinal changes and calcification in the skin, arteries, and heart; and retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations known as RVCL-S (*TREX1*). These conditions often affect younger patients than those affected by common strokes.

Fabry disease, for example, is an X-linked lysosomal storage disease caused by a deficiency of α-galactosidase. This results in a pathologic accumulation of unmetabolized lipids in many cell types. In hemizygous males, the condition classically presents in childhood or adolescence with skin findings (angiokeratomas), corneal opacities (cornea verticillata), and a painful neuropathy (acroparesthesias). In adulthood, additional manifestations unfold including cardiac dysfunction with left ventricular thickening, kidney disease, and systemic vasculopathy leading to stroke and transient ischemic attacks. Heterozygous females can also present with symptomatic enzyme deficiency, leading to delayed or heterogeneous phenotypes. Enzyme replacement therapy is indicated for individuals who are clinically symptomatic with a confirmatory genetic diagnosis. Enzyme replacement therapy has been shown to be beneficial for systemic complications, though the effect on stroke risk reduction has yet to be confirmed.

As outlined in this chapter, stroke can result from a variety of medical conditions, toxins, sex-related risk factors, and genetic predispositions. The majority of ischemic strokes occur due to a cumulative effect from hypertension, diabetes mellitus, hyperlipidemia, and atrial fibrillation. However, stroke can manifest in patients independent of these traditional risk factors and thus an understanding of the expanse of conditions with potentially distinct treatment options is crucial to stroke prevention.

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SECTION

2

Gastrointestinal Tract and Related Disorders

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CHAPTER

12

Hepatic and Pancreatic Encephalopathy

KARIN WEISSENBORN

HEPATIC ENCEPHALOPATHY
- Definition
- Clinical Features
  - *Chronic Progressive Hepatic Encephalopathy*
  - *Minimal Hepatic Encephalopathy*
  - *Encephalopathy in Acute Liver Failure*
- Diagnosis of Forms of Hepatic Encephalopathy
  - *Cirrhosis-Related Parkinsonism*
  - *Hepatic Myelopathy*
  - *Minimal Hepatic Encephalopathy*
  - *Increased Intracranial Pressure in Acute Liver Failure*
- Neuroimaging
- Laboratory Studies
- Pathophysiology
- Treatment
  - *Hepatic Encephalopathy in Cirrhosis*
  - *Minimal Hepatic Encephalopathy*
  - *Cirrhosis-Related Parkinsonism and Hepatic Myelopathy*
  - *Hepatic Encephalopathy in Acute Liver Failure*

PANCREATIC ENCEPHALOPATHY
- Definition and Clinical Features
- Diagnosis
- Treatment

HEPATIC ENCEPHALOPATHY

Definition

The term *hepatic encephalopathy* (HE) refers to any type of cerebral dysfunction that is due to liver insufficiency and/or portosystemic shunting and is detectable by clinical, neuropsychologic, or neurophysiologic means. Three types of HE are differentiated based on the underlying cause: type A occurs in patients with acute liver failure (ALF), type B in patients with portosystemic shunting in the absence of liver dysfunction, and type C in patients with cirrhosis. Episodic, recurrent, and chronic progressive forms have been described.[1]

Clinical Features

HE is characterized by alterations of cognition, motor function, and consciousness in various combinations.[2] The most commonly used grading system that distinguishes grades of HE (I–IV) based on the degree of alteration in consciousness is the West Haven system (Table 12-1). Motor symptoms can be detected in all grades, but with increasing frequency and severity in grades II and III (Fig. 12-1). The most characteristic motor findings are extrapyramidal and cerebellar symptoms, including hypomimia, hypo- and bradykinesia, rigidity, tremor, dysarthria, dysdiadochokinesia, and ataxia. Hyperreflexia and pyramidal signs are observed predominantly in patients with grades III and IV encephalopathy. Asterixis (flapping tremor), a form of negative myoclonus, may be present in the absence of any alteration of consciousness or cognition, but is observed most frequently in patients with grade II or III disease.

Difficulties in writing and speech disturbances are some of the first symptoms of HE in patients with liver cirrhosis. In the early phases, tremulous writing, omission of single letters, reversal of order, and misspellings are common. With later stages of HE, letters become superimposed and lines of writing converge. Patients become unable to sign their names or to move the pencil from left to right. Speech, initially monotonous and slowed, becomes slurred and unintelligible with associated dysphasia in later stages of the illness.

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Personality changes and alterations of mood may be the first symptoms of HE and are generally first observed by relatives or friends. As the disease progresses, patients may become uninhibited and bizarre due to increasing difficulties in visual perception and disorientation, illusions, and hallucinations. Mood alterations including euphoria and depression are common and may exhibit rapid fluctuations.

TABLE 12-1 ■ West Haven Criteria for Grading of Clinically Overt Hepatic Encephalopathy

Grade I	Trivial lack of awareness, shortened attention span, impaired performance of addition, euphoria or anxiety
Grade II	Lethargy or apathy, minimal disorientation for time and place, inappropriate behavior
Grade III	Somnolence to semistupor but responsiveness to verbal stimuli, confusion, gross disorientation
Grade IV	Coma

From Ferenci P, Lockwood A, Mullen K, et al: Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 35:716, 2002, with permission.

CHRONIC PROGRESSIVE HEPATIC ENCEPHALOPATHY

The chronic progressive (or persistent) form of HE has predominantly been observed in patients with extensive portosystemic shunting that developed either spontaneously or after transjugular intrahepatic portosystemic stent shunting or other shunting procedures. Data regarding the prevalence of this subtype of HE are sparse. Cirrhosis-related parkinsonism and hepatic myelopathy are the best characterized manifestations of this form of HE. In a prospective study of 214 patients with cirrhosis awaiting liver transplantation, cirrhosis-related parkinsonism was found in 4 percent and hepatic myelopathy in 2 percent of patients.[3] The parkinsonian patients show hypomimia, hypokinesia, tremor, and rigidity similar to patients with idiopathic Parkinson disease (PD), but typically they do not develop the characteristic shuffling gait of PD and have predominant involvement of their upper limbs. Moreover, symptoms develop faster and are symmetric more often. Tremor occurs predominantly with action; a parkinsonian rest tremor is observed less commonly. The extrapyramidal symptoms may be associated with cerebellar and corticospinal deficits.

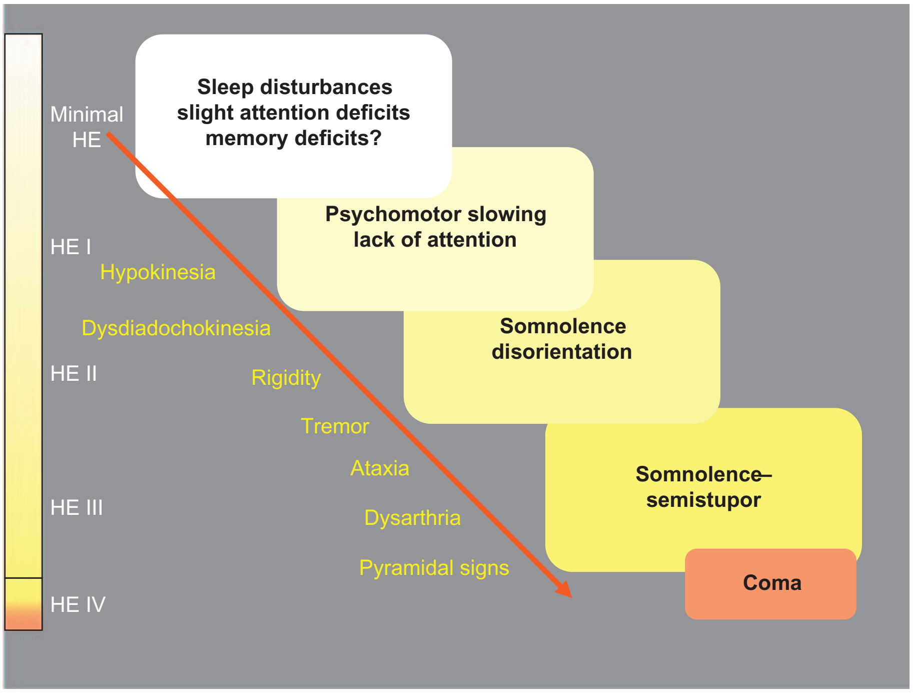

FIGURE 12-1 ■ Hepatic encephalopathy (HE) should be considered as a continuum of decreasing brain function rather than a sequence of well-defined steps of cerebral alteration. To compare different patient groups, however, grading systems such as the West Haven criteria have been developed, which subdivide patients with HE into groups depending on the extent of any alteration of consciousness. Motor symptoms of HE may be present in all grades, even in the absence of cognitive dysfunction.

Some patients present with a combination of cirrhosis-related parkinsonism and hepatic myelopathy. The myelopathy is characterized by a rapidly progressive spastic paraparesis without accompanying sensory deficits or disturbances of bladder or bowel functions.[2,3] After only a few months of progressive disability, most patients with hepatic myelopathy either depend upon an assistive device or are confined to a wheelchair. For unknown reasons most patients with hepatic myelopathy are men, whereas cirrhosis-related parkinsonism is equally prevalent in men and women.[2,3]

MINIMAL HEPATIC ENCEPHALOPATHY

Minimal HE is considered the mildest form of HE and is defined as cerebral dysfunction detectable only by neuropsychologic or neurophysiologic means in the absence of clinically overt symptoms of encephalopathy. The concept of minimal HE was developed in the 1970s when it became obvious that some patients who were considered unimpaired clinically nevertheless had significant deficits in attention, visual perception, and motor speed and accuracy on neuropsychometric tests; some only showed slowing of the electroencephalogram (EEG). These observations led to the addition of this early stage of HE to established grading systems.[1,2]

The prevalence of minimal HE ranges between 30 and 60 percent of patients with liver cirrhosis. Variations in prevalence estimates are due to differences in methods used for diagnosis and population differences regarding underlying liver diseases.

It has been suggested that minimal and grade I HE should be merged into a new class termed “covert HE” as grade I HE may only be apparent to clinicians with experience in neurologic assessment.[1] More detailed clinical examination of HE patients yields a higher number with grade I HE and fewer with minimal HE. In one study, among patients initially thought to be clinically unimpaired, bradykinesia, tremor, and hyperactive muscle stretch reflexes were detected in about 30 percent when examined in detail, and 50 percent of these patients showed eye movement abnormalities indicating cerebellar dysfunction.[2]

ENCEPHALOPATHY IN ACUTE LIVER FAILURE

The presence of HE is a prerequisite for diagnosing ALF in patients with jaundice, coagulopathy, and no pre-existing liver disease. Thus, HE is present by definition in all patients with ALF.[4] In contrast, clinically overt HE is prevalent in 10 to 14 percent of all cirrhotic patients, and in about 20 percent of patients with decompensated cirrhosis.[1] The risk of HE recurrence is 40 percent within 1 year.

In contrast to HE in patients with liver cirrhosis, HE with ALF may be complicated by significant brain edema (25 to 35% in grade III; 65 to 75% in grade IV). Currently, the prevalence of brain edema in patients with ALF seems to be decreasing, though for unclear reasons. An analysis of the case records of 3,305 patients with ALF or acute liver injury from King’s College Hospital, London, between 1973 and 2008 showed that the proportion of patients with intracranial hypertension fell from 76 percent in the period from 1984 to 1988 to 20 percent in 2004 to 2008. Multivariate analysis showed an association of intracranial hypertension with younger age, female sex, and elevated international normalized ratio.[4]

While restlessness, agitation, and irritability are characteristic of the initial phase of ALF, HE in patients with cirrhosis usually begins with psychomotor slowing. With increasing grade of HE, clinical presentations are more similar, as depressed consciousness predominates. Extrapyramidal symptoms are not typically observed in patients with ALF, but signs of corticospinal tract dysfunction are present. Seizures are a frequent complication of ALF, but occur only rarely in patients with cirrhosis.

Diagnosis of Forms of Hepatic Encephalopathy

The diagnosis of HE can only be made after exclusion of other possible causes of brain dysfunction, as the symptoms are not specific. Hyponatremia, hypo- or hyperglycemia, uremia, diabetes mellitus, and renal dysfunction are frequent in patients with cirrhosis and may resemble HE. Other important disorders to distinguish are septic encephalopathy and Wernicke encephalopathy.[1] In a neuropathologic study of the brains of 32 patients with cirrhosis who died with HE, cerebellar lesions suggestive of Wernicke encephalopathy were observed in 50 percent. The diagnosis of Wernicke encephalopathy was made in nine patients, whereas it had been made based on clinical findings in only two patients.[2]

Due to altered coagulation, intracranial hemorrhage must be considered in the differential diagnosis of HE, and brain imaging should be obtained in all patients, usually with noncontrast computed tomography (CT). Magnetic resonance imaging (MRI) requires much more cooperation than CT, and thus is not practical in agitated patients.

Cirrhosis-Related Parkinsonism

In patients with cirrhosis who develop clinical signs of extrapyramidal motor dysfunction, the differential diagnosis includes acquired hepatocerebral degeneration or an independent neurodegenerative disease. The course of the disease and the symptom combination may help to differentiate between these entities.[3]

The clinical features of cirrhosis-related parkinsonism resemble those of patients with PD. As discussed earlier, however, symptoms in PD are more often asymmetric, develop more slowly, may be associated with early gait abnormalities, are not accompanied by cerebellar or corticospinal deficits, and respond well to dopaminergic drugs.

More difficult is the distinction from multiple system atrophy (MSA), which combines extrapyramidal symptoms with cerebellar and pyramidal deficits and thereby can resemble cirrhosis-related parkinsonism. MSA likewise shows rapid progression and often a poor response to dopaminergic agents. In contrast to patients with cirrhosis-related parkinsonism, however, patients with MSA characteristically show severe autonomic dysfunction and many show alterations of the basal ganglia, midbrain, and cerebellum on MRI. Single-photon emission computed tomography (SPECT) in patients with cirrhosis-related parkinsonism shows a decreased binding capacity of striatal dopamine receptors and the dopamine transporter similar to the findings in MSA but different from those in PD, in which there is decreased availability of the transporter but not of the receptors.

Hepatic Myelopathy

A diagnosis of hepatic myelopathy can be based on the clinical findings of myelopathy and exclusion of other possible causes through MRI and cerebrospinal fluid analysis, both of which are normal in hepatic myelopathy.[3]

Minimal Hepatic Encephalopathy

The diagnosis of minimal HE depends on the results of neuropsychologic or neurophysiologic examinations in the setting of a normal clinical examination.[5–7] Debate about the most useful method for diagnosing minimal HE is ongoing. Currently the Portosystemic Encephalopathy (PSE) Syndrome Test, Inhibition Control Test, critical flicker frequency analysis, and automated EEG analysis are the most frequently used methods. A combination of the number connection tests A and B and either the digit symbol test or the block design test, or both, are used as an alternative. Working groups commissioned to elaborate an expert recommendation for diagnosing minimal HE agreed on the PSE Syndrome Test as valuable, objective, and reliable.[5] For the United States, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) has been recommended as an alternative, because it is a valid, objective, and reliable test battery, and there are no US norms for the PSE Syndrome Test.[5] However, the RBANS has only rarely been used for diagnosing minimal HE, and thus data regarding its suitability for this purpose are sparse.

The PSE Syndrome Test is a battery of five paper-pencil tests: the number connection tests A and B, the digit symbol test, the serial dotting test, and the line-tracing test.[1,5] The latter is evaluated by measuring the time needed to perform the test and the number of errors that occur. Thus, six subtest results are scored compared to normative values. A sum score termed the portosystemic hepatic encephalopathy score (PHES) is generated ranging between +6 and −18 points; according to current German norms, scores lower than −4 are considered abnormal. Of note, local norms differ significantly, and thus must be determined for every population before the test is used for diagnosing minimal HE. The PHES correlates significantly with cerebral glucose utilization at rest in patients with minimal HE. It is a reliable predictor of the risk of both, overt HE and mortality in patients with liver cirrhosis.

The critical flicker frequency is a psychophysiologic test that has been used in the past for the assessment of central nervous system drug effects. It was recommended for diagnosing minimal HE in 2002. Light pulses are presented to the subject in decreasing frequency (usually from 60 Hz downwards), and the subject has to react as soon as the impression of fused light switches to flickering light. The critical flicker frequency depends on the experimental setting—the color and luminance of the stimuli, distance between the light source and the subject's eye, visual angle, and age. The assessment requires intact binocular vision and absence of red-green blindness. Normative data have to be elaborated for the specific equipment used. The results correlate with the PHES and can predict the development of overt HE. Of note, critical flicker frequency depends on age, and thus age-adjusted norms should be used for the evaluation of results. Moreover, scores in patients with alcoholic cirrhosis are lower than in patients with cirrhosis due to other causes. The results may also be affected by propofol given during endoscopy, though only temporarily.

The Inhibitory Control Test (ICT) has been recommended for diagnosing minimal HE as well. It is freely available online (www.hecme.tv) and is a test of attention and response inhibition. Results depend on age and education and must be compared with normative values.

The Continuous Reaction Time Test (CRT) requires a simple reaction to a series of 500-Hz tones. With developing HE, not only reaction time but especially the variability of reaction times increases. The reaction time variability is represented by the so-called CRT index, which is calculated from the fiftieth reaction time percentile/(90th − 10th percentile). Recently it was shown that the CRT index does not depend on age or sex, and is more sensitive for cerebral dysfunction in patients with liver cirrhosis than the critical flicker frequency test.

The EEG has been used for diagnosing HE for decades after it had been observed that the amount of theta and delta activity increases with increasing grade of HE. This alteration is associated initially with an increase in amplitude and the appearance of triphasic waves, followed in later stages by a decrease in amplitude, a discontinuous pattern, and finally isoelectricity in patients with coma (Fig. 12-2).[6] Occasionally the EEG is unaltered in spite of

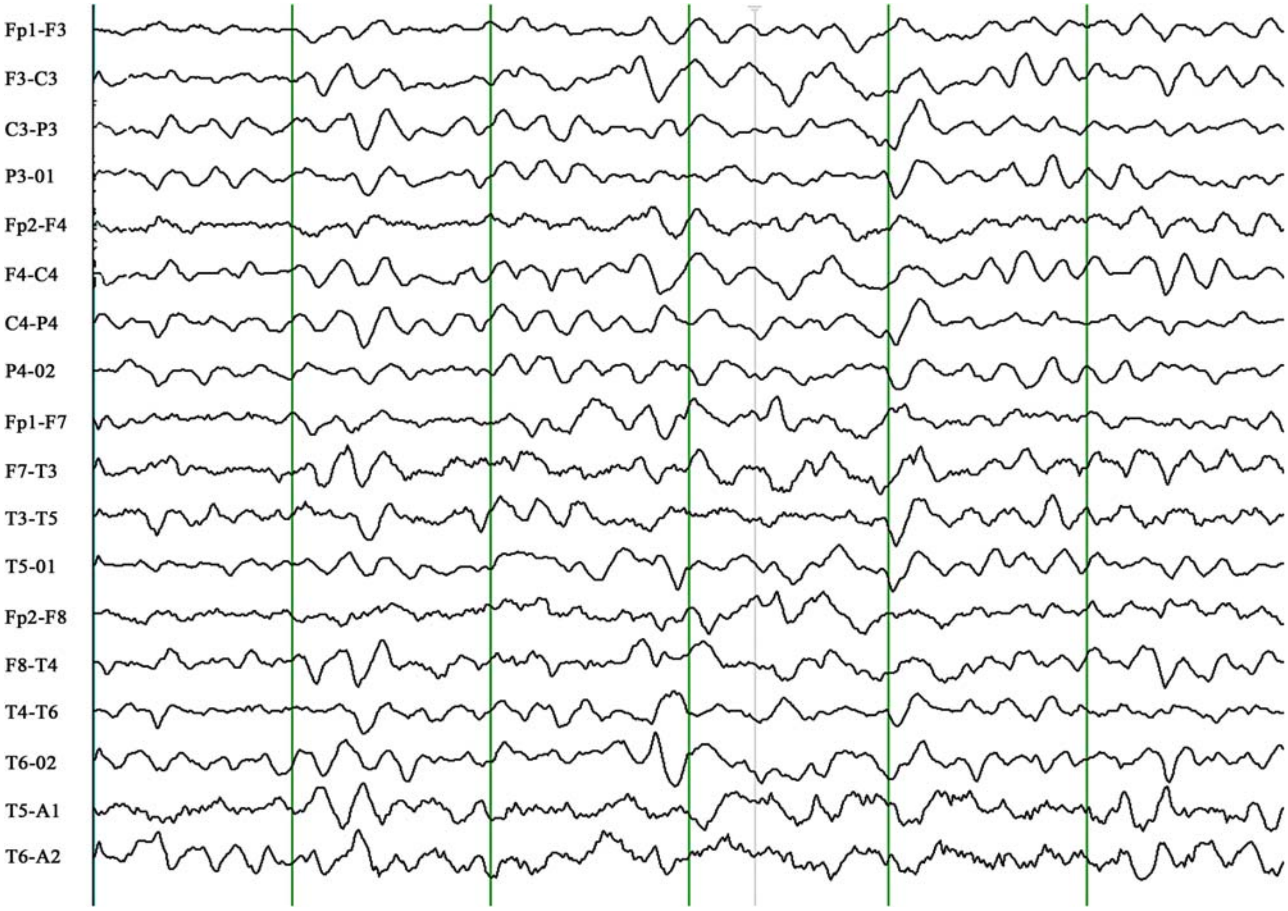

FIGURE 12-2 ▪ The EEG of a patient with hepatic encephalopathy (grade II according to the West Haven criteria). The portosystemic hepatic encephalopathy score was −17. The EEG shows diffuse slow activity (mean dominant frequency 4.49) with triphasic components. Time marker, 1 second.

clinically overt HE. Quantitative EEG analysis shows a decrease in the mean dominant frequency and an increase in theta and delta activity in only 15 to 30 percent of patients with cirrhosis having no clinical signs of HE, and in up to 40 percent of patients with clinically overt HE. Thus EEG appears more appropriate for serially following the progression of HE than for diagnosis.

Computerized EEG analysis continues to be refined, but diagnostic utility is limited at this time.

INCREASED INTRACRANIAL PRESSURE IN ACUTE LIVER FAILURE

The percentage of patients with brain edema and increased intracranial pressure (ICP) increases with more severe grades of HE in patients with ALF.[4] Since intubation and sedation are required in these patients, brain edema cannot always be detected by clinical examination. Repeated brain imaging may show the development of cerebral edema but is not feasible. Continuous monitoring of ICP is recommended by some clinicians, but the coagulopathy that accompanies ALF holds a significant risk of intracranial bleeding. As a result, ICP monitoring is not standard in the management of patients with ALF. Studies have shown no difference in mortality between patients who underwent or did not undergo ICP monitoring.

Neuroimaging

Brain imaging in HE is used to exclude other possible causes of brain dysfunction such as intracranial hemorrhage or Wernicke encephalopathy. MRI, however, may not be feasible in HE patients because of lack of cooperation due to alterations of consciousness.

Although MRI of the brain in patients with cirrhosis shows characteristic symmetric signal change with predominance in the pallidum on T1-weighted sequences, these MRI findings cannot be used to diagnose HE since some patients may show signal change with no signs of HE and others may be severely affected by HE without MRI abnormalites.[1] These MRI changes are thought to be due to deposition of manganese in the brain and correlate with serum manganese levels in patients with cirrhosis. It is still controversial whether the extent of MRI signal change is related to the extent of extrapyramidal symptoms. Of note, the MRI changes fade over about 1 year following successful liver transplantation, while the clinical symptoms of HE usually disappear immediately.

Laboratory Studies

There are no laboratory parameters that can be used for diagnosing HE. Plasma ammonia levels follow the clinical course in an individual patient, but there is no clear correlation between ammonia levels and the degree of HE.[1,2] However, if plasma ammonia is normal in a patient with liver cirrhosis and severe alteration of consciousness, the diagnosis of HE should be questioned.

Pathophysiology

The pathophysiology of HE is still incompletely understood. Currently, hyperammonemia and increased levels of inflammatory cytokines are considered to play a major role.[8,9] Blood ammonia levels may increase in patients with liver cirrhosis up to 300 μmol/L, but range between normal levels (up to 40 μmol/L) and 100 μmol/L in the majority of patients.[1,2] Although there is a correlation between plasma ammonia level and the grade of HE, there is substantial overlap, indicating that other factors besides hyperammonemia play a role in the development of HE. Increased blood ammonia levels are accompanied by an increase in cerebral ammonia concentration; in the brain, ammonia is detoxified in astrocytes by glutamine synthesis. Increased cerebral ammonia levels induce glutamine synthase activity, glutamate uptake, and glutamine production leading to osmotic pressure and water uptake. Inhibition of glutamine release from astrocytes due to a downregulation of glutamine transporters adds to cell swelling unless other osmolytes such as *myo*-inositol are released in compensation.

Astrocyte swelling is considered the key factor in the pathogenesis of HE as it triggers multiple alterations of cell function and gene expression.[8,9] Astrocyte swelling induces the formation of reactive oxygen and nitrogen oxide species, including nitric oxide (NO), which in turn induce further astrocyte swelling. Part of this cycle leads to a collapse of the mitochondrial inner membrane potential, swelling of the mitochondrial matrix, defective oxidative phosphorylation, cessation of adenosine triphosphate synthesis, and finally the generation of reactive oxygen species.

HE in patients with cirrhosis is often precipitated by electrolyte disturbances, benzodiazepines, or infection. Astrocyte swelling may be induced also by inflammatory cytokines, hyponatremia, or benzodiazepines.[8,9] The vulnerability of the brain to these precipitating factors depends on the amount of astrocytic osmolyte depletion that has taken place prior to the insult; for example, lower *myo*-inositol levels increase the risk of developing neuropsychiatric symptoms in response to a protein load.

The toxic effects of ammonia and inflammatory cytokines are amplified by intracerebral manganese deposition in patients with hepatic cirrhosis, due to impaired biliary manganese excretion. Manganese increases ammonia toxicity in astrocyte cultures and alters dopaminergic neurotransmission. Brain autopsy examinations show that manganese deposition causes cell loss and gliosis in the globus pallidus, caudate, putamen, and subthalamic nucleus.

HE in its episodic form is not accompanied by significant neuronal alterations, but the size and number of Alzheimer type II astrocytes increases. The extent of this astrocytosis correlates with the severity of HE and blood ammonia levels. Neuronal cell death is considerably less than would be expected considering the numerous cell death mechanisms present in this condition, such as NMDA receptor-mediated excitotoxicity, oxidative/nitrosative stress, and the presence of proinflammatory cytokines. It has been hypothesized that the extent of neuronal damage in liver failure may be attenuated by compensatory mechanisms including downregulation of NMDA receptors or the presence of neuroprotective steroids such as allopregnanolone. In contrast to patients with episodic HE, patients with acquired hepatocerebral degeneration show neuronal degeneration in the deep layers of cerebral cortex and subcortical white matter, particularly in the parieto-occipital cortex, basal ganglia, and cerebellum. The reason that some patients are more susceptible than others to progressive neuronal degeneration is unknown.

In patients with ALF, blood ammonia levels are markedly increased and correlate with high ICP, severity of clinical presentation, and death due to cerebral herniation.[4] However, ammonia-lowering strategies working in type C HE have not been shown to be effective in treating HE and brain edema in ALF.[4] Additional mechanisms of injury may involve proinflammatory cytokines; serum levels of tumor necrosis factor-α (TNF-α) and interleukin 6 are invariably increased in ALF patients and relate to the severity of HE. The presence of a systemic inflammatory response syndrome (SIRS) has been identified as a predictor of HE progression in patients with ALF due to acetaminophen overdose. Current models explaining brain dysfunction in ALF suggest a simultaneous reaction between systemic proinflammatory cytokines and a neuroinflammatory response to the increase of cerebral ammonia, with a corresponding increase in cerebral lactate level. The cause of the increased lactate level is not known—it was previously thought to be the consequence of an alteration of energy metabolism but currently is attributed to an altered astrocyte–neuron lactate shuttle, as high-energy phosphate levels are unaltered in animal models of ALF.

The reasons for the development of increased ICP in ALF are still unclear. Cytotoxic cerebral edema occurs in ALF, but the occurrence of vasogenic edema is controversial. Pathologic studies of patients who died with ALF have not shown evidence of a breakdown of the blood–brain barrier. However, in patients with ALF and a concomitant infection or sepsis, blood–brain barrier breakdown may occur as it does in many forms of septic encephalopathy. An increase in cerebral blood flow due to an alteration of cerebrovascular autoregulation may also play a role in the development of increased ICP in ALF.

Treatment

Hepatic Encephalopathy in Cirrhosis

Most HE episodes in patients with cirrhosis are precipitated by medications such as diuretics or sedatives, excessive protein intake, gastrointestinal bleeding, or infection. Correction of these precipitating factors is the basis of any initial therapy in these patients. In addition, treatment with drugs that reduce gut ammonia production and absorption is recommended. The most frequently administered medication for this purpose is lactulose. Its use has been supported in a recent meta-analysis of randomized controlled trials of nonabsorbable disaccharides (lactulose/lactitol) versus placebo/no intervention.[10] This showed a beneficial effect of nonabsorbable disaccharides on mortality and treatment as well as on prevention of HE. In addition, this meta-analysis found evidence that treatment with lactulose improves cognitive function and probably also quality of life in patients with minimal HE. The initial dose should be 50 ml of lactulose syrup every 1 to 2 hours until at least two bowel movements are produced. Thereafter, the dose should be reduced to produce two to three bowel movements per day (30 to 60 g or 45 to 90 ml daily).

When a patient's condition does not improve with lactulose, and concomitant disorders that might impair brain function have been excluded, lactulose should be combined with antibiotics, which also reduce gut ammonia production and absorption. In the past, neomycin and, alternatively, metronidazole were used predominantly, but nowadays rifaximin is used; it has minimal side effects and good efficacy in the treatment as well as secondary prevention of HE.[11]

In some countries, L-ornithine L-aspartate (LOLA) is used as second-line therapy for the treatment or prevention of overt HE, and predominantly in conjunction with lactulose. Data on its efficacy are sparse. The authors of a recent meta-analysis concluded that LOLA might have a beneficial effect on mortality, HE, and serious adverse events in comparison with placebo or no intervention, but they rated the quality of evidence as very low and recommended further trials.[12] Branched-chain amino acids (BCAA) have also been used for treating HE but have not yet found general acceptance. A meta-analysis including 16 randomized clinical trials where BCAA were compared to either placebo, no intervention, diets, lactulose, or neomycin, however, showed beneficial effects of oral BCAA treatment upon HE, while there was no effect on mortality.[13]

Prevention of Further Spells

Although lactulose is frequently used for the prevention of HE episodes, data supporting its use for this purpose are scant. A single-center, unblinded, randomized-controlled study showed less recurrence of HE with lactulose therapy than with placebo. This positive effect was also observed in cirrhotic patients with gastrointestinal bleeding. In one study, lactulose, probiotics, and no therapy were compared for prevention in 235 patients who had recovered from an HE episode. Both lactulose and probiotics were significantly more effective than no therapy in preventing a further HE episode during a 12-month follow-up period. A positive effect of lactulose for preventing HE episodes was also shown in patients with cirrhosis without a history of overt HE, supporting its use for primary prevention. Among the patients, 55 percent had minimal HE. Minimal HE responded to lactulose in 66 percent of cases, while improving spontaneously in only 25 percent. A recent review summed up the results of eight trials with lactulose for the prevention of overt HE, and showed that long-term lactulose therapy prevents recurrence of overt HE. Another six trials showed that addition of rifaximin to lactulose significantly reduced the recurrence of overt HE and rate of HE-related hospitalizations in comparison with lactulose therapy alone.[11] In clinical practice, routine long-term treatment with lactulose is jeopardized by noncompliance of patients due to gastrointestinal side effects. A switch to rifaximin monotherapy may be considered in these patients, but further research is needed to back up this strategy.

MINIMAL HEPATIC ENCEPHALOPATHY

Treatment of minimal HE is controversial, and data on the therapeutic effects of drugs are sparse. Since cognitive changes significantly impair the quality of life of patients and their relatives, many physicians consider treating these patients, and this strategy is supported by the results of a recent meta-analysis of various treatment studies in patients with minimal HE.[14] According to this analysis, lactulose is effective in treating minimal HE, preventing overt HE, lowering ammonia levels, and improving health-related quality of life. Rifaximin and lactulose were the most effective drugs for reversal of minimal HE while—compared to placebo or no treatment—LOLA, lactulose, and probiotics significantly reduced the risk of developing overt HE.

CIRRHOSIS-RELATED PARKINSONISM AND HEPATIC MYELOPATHY

Cirrhosis-related parkinsonism does not respond to ammonia-lowering therapies but may respond to dopaminergic drugs.[3] Liver transplantation is also sometimes helpful, but only a few cases have been reported. Patients unresponsive to lactulose may improve with rifaximin therapy. Hepatic myelopathy similarly fails to respond to ammonia-lowering therapies but liver transplantation may lead to an improvement in walking ability.[3]

Hepatic Encephalopathy in Acute Liver Failure

In patients with ALF, treatment of HE and brain edema is aimed at reducing levels of plasma ammonia and systemic cytokines.[4] A basic treatment strategy is the prophylactic use of antibiotics and antifungals along with early continuous renal replacement therapy to allow highly efficacious ammonia removal. Persistent hyperammonemia above 122 μmol/L for more than 3 days is associated with an increased risk of developing brain edema, seizures, and death. Drugs that are used for the reduction of plasma ammonia levels in patients with cirrhosis such as lactulose or LOLA have not shown a significant beneficial effect in ALF. Lactulose treatment is discouraged because gaseous distension of the bowel may impede liver transplantation surgery.

Hyponatremia is one of the causes of brain edema and intracranial hypertension in patients with ALF. Therefore normalization and even a slight elevation of plasma sodium levels up to 155 mEq/L (mmol/L) is recommended. ICP has been shown to decrease significantly in patients in whom serum sodium levels were maintained in a range of 145 to 155 mEq/L (mmol/L).

Moderate hypothermia (32° to 34°C) has been demonstrated to reduce plasma levels of proinflammatory cytokines and elevated ICP in patients awaiting emergency liver transplantation, and thus may be considered as bridging therapy in patients with uncontrolled intracranial hypertension before transplantation. Considering the negative results of a randomized controlled study, induction of moderate hypothermia for prevention of intracranial hypertension is not recommended.[4]

Brain edema in patients with ALF is currently treated with mannitol infusion every 6 hours (1 g mannitol/kg body weight) or, in cases with ICP monitoring, in response to ICP increases above 20 to 25 mmHg; mannitol should be held if serum osmolality exceeds 320 mOsm/L or in patients with oliguric renal dysfunction. ICP monitoring is often not feasible due to severe coagulopathy.

To maintain a sufficient cerebral perfusion pressure of 60 to 80 mmHg, mean arterial blood pressure should be raised in patients with hypotension to greater than 75 mmHg through repletion of intravascular volume with normal saline and the use of vasopressors (e.g., vasopressin and norepinephrine). One of the most important tasks in the treatment of patients with ALF is the identification of those who will need liver transplantation; the King's College criteria are frequently used for this purpose.[4]

PANCREATIC ENCEPHALOPATHY

Definition and Clinical Features

Pancreatic encephalopathy is a controversial entity consisting of a confusional state due to acute pancreatitis. The underlying pathophysiology remains unclear. Since acute pancreatitis is accompanied by the SIRS, electrolyte abnormalities, hypotension, renal failure, acute respiratory distress syndrome, disseminated intravascular coagulation, and hyperglycemia, all of which can induce brain dysfunction, the delineation of a discrete disease is difficult.[15] There is some evidence that pancreatic enzymes themselves are involved in the development of a metabolic encepalopathy. The activation of phospholipase A by trypsin and bile acid likely plays a key role in the pathophysiology of pancreatic encephalopathy. Activated phospholipase A converts lecithin and cephalin into their hemolytic forms. Phospholipase A and hemolytic lecithin then may destroy the blood–brain barrier, resulting in demyelination, hemorrhage, and edema due to increased vascular permeability. Neuropathologic studies of patients who died with pancreatic encephalopathy show capillary necrosis with diffuse petechial hemorrhages, encephalomalacia, and perivascular demyelination.

Pancreatic encephalopathy usually begins within 2 weeks after the onset of acute pancreatitis, most often between the second and fifth days. Clinical symptoms, which may fluctuate, include disorientation, confusion, agitation, anxiety, irritability, delirium, hallucinations, dysarthria, ataxia, akinetic mutism, rigidity, hemiparesis, hyperreflexia, and seizures. Patients may develop stupor and coma. In a 7-year follow-up case report, recurrence of neurologic symptoms occurred with each relapse of pancreatitis, and a close relationship was found between serum amylase levels and the occurrence of neurologic symptoms. Neuropsychiatric symptoms do not correlate in severity with the pancreatitis, and improvement of these symptoms may lag behind recovery from pancreatitis. The mortality rate from pancreatic encephalopathy is estimated to be as high as 50 percent.

Diagnosis

Pancreatic encephalopathy should be suspected in any patient with severe abdominal pain and altered consciousness. Since neither symptoms nor laboratory or imaging results are specific for the disorder, the diagnosis can only be made after exclusion of other possible causes of brain dysfunction. The EEG typically shows generalized slowing. The cerebrospinal fluid may show a mild increase in protein and glucose concentration, but is normal in most cases. In a few cases, lipase concentrations in the cerebrospinal fluid have been assessed and were slightly elevated. There are only a few reports of brain MRI findings in patients with pancreatic encephalopathy and these describe predominantly diffuse or scattered white matter abnormalities. Abnormalities of the pons and cerebellar peduncles have been seen on diffusion-weighted and fluid-attenuated inversion recovery sequences. A case of pancreatic encephalopathy associated with pontine and extrapontine myelinolysis involving the brain and spinal cord has been described.

Treatment

There are no standard recommendations for the treatment of pancreatic encephalopathy other than supportive therapy along with treatment of the underlying pancreatitis. In one study, a significant decrease was found in the frequency of pancreatic encephalopathy in patients with acute pancreatitis treated with low-molecular-weight heparin compared to a control group. This effect may result from a reduction in pancreatitis-associated microvascular disturbances and hemorrhagic necrosis.

Patients with pancreatitis are also at risk of developing Wernicke encephalopathy due to hyperemesis, anorexia, and the necessity of prolonged total parenteral nutrition. Thiamine deficiency should be considered in these patients and treated prophylactically.

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CHAPTER

13

Other Neurologic Disorders Associated with Gastrointestinal Disease

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GASTROINTESTINAL DISORDERS
- Bariatric Surgery
- Celiac Disease
  - *Ataxia*
  - *Peripheral Neuropathy*
  - *Myopathy*
  - *Epilepsy*
  - *Other Manifestations*
- Inflammatory Bowel Disease
  - *Peripheral Neuropathy*
  - *Demyelinating Disease*
  - *Cerebrovascular Disease*
  - *Myopathy*
  - *Myelopathy*
  - *Other Manifestations*
- Whipple Disease
- Malabsorption Syndromes
  - *Vitamin E Deficiency*
  - *Familial Hypocholesterolemia*
  - *Tropical Sprue*
  - *Wernicke Encephalopathy*
  - *Pellagra*
  - *Copper Deficiency*

HEPATIC DISORDERS
- Wilson Disease
  - *Pathophysiology*
  - *Clinical Presentation*
  - *Diagnosis*
  - *Treatment*

The presence of gastrointestinal (GI) dysfunction in the setting of neurologic disease has received increasing attention in recent years, particularly in disorders such as Parkinson disease. Much less attention has been devoted to the occurrence of neurologic dysfunction in primary GI disease processes. The enteric nervous system (ENS), which lines virtually the entire GI tract, contains approximately the same number of neurons as the spinal cord and is capable of generating and controlling many functions entirely independently of the central nervous system (CNS). It should not be surprising, then, that processes affecting the GI system, including the ENS, also may affect the CNS or systems controlled by the CNS.

GASTROINTESTINAL DISORDERS

Bariatric Surgery

The increasing prevalence of obesity worldwide has led to immense growth in bariatric surgery, which typically is performed after behavioral modification, medical nutrition therapy, and physical activity enhancement strategies have failed. The number of bariatric operations performed in the United States has increased over the past three decades, and the American Society for Metabolic and Bariatric Surgery estimates that up to 228,000 procedures were performed in 2017 alone.[1] Different methods of surgical intervention, including gastric restriction procedures (e.g., laparoscopic adjustable gastric banding, sleeve gastrectomy, vertical banded gastroplasty), malabsorptive procedures (e.g., biliopancreatic diversion, jejunoileal bypass), and combined restrictive and malabsorptive procedures (e.g., Roux-en-Y gastric bypass, duodenal switch with biliopancreatic diversion) have been performed frequently, but sleeve gastrectomy, in which approximately 75 to 85 percent of the stomach is removed along the greater curvature, is particularly growing in popularity. Neurologic complications may occur following all of these procedures, both in the immediate perioperative period and months to years after the surgery.

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Neurologic complications occur in a range of 3 to 16 percent following these procedures. Although peripheral nervous system disorders appear to be the most frequent neurologic complications, encephalopathy, myelopathy, and optic neuropathy all have been reported. The mechanisms of neural injury following bariatric surgery include both mechanical compression and entrapment leading to mononeuropathies as well as nutritional deficiencies. Rapid weight loss can lead to loss of protective fat pad and compression through loss of subcutaneous tissue. Injury from mechanical retractors or malpositioning during surgery can lead to immediate complications after bariatric surgery. The most important factors in the pathogenesis of neurologic complications are nutritional deficiencies, often due to malabsorption or prolonged emesis.

Three patterns of peripheral neuropathy have been described following bariatric surgery: sensory-predominant polyneuropathy, mononeuropathy, and radicular or plexus neuropathy. Peripheral neuropathy is reported in over 15 percent of patients following bariatric surgery, compared with only 3 percent of patients undergoing cholecystectomy. In a subsequent cohort drawn from a single tertiary referral center, investigators noted peripheral neuropathy in only 7 percent but did not report on the frequency of other types of neurologic complications.[2] Peripheral neuropathy typically is chronic, although acute inflammatory demyelinating polyneuropathy also has been reported. Carpal tunnel syndrome is the most frequent mononeuropathy, accounting for 80 percent of cases. Lateral femoral cutaneous neuropathy (meralgia paresthetica) develops in only around 1 percent of individuals despite recent weight loss being a well-known risk factor for its development. Peroneal neuropathy leading to numbness and weakness in the affected leg can manifest as "foot drop" and pose functional limitations to the patient. Risk factors include marked weight loss, rapid rate of weight loss, and postoperative complications.

Nutritional deficiencies (see Chapter 15) due to malabsorption are responsible for the development of neuropathy in many, although not all, instances. Deficiencies of riboflavin, pyridoxine, vitamin B_{12}, folate, vitamin D, vitamin E, and copper all have been described. Thiamine deficiency, one of the most common and serious complications of bariatric surgery, can lead to Wernicke encephalopathy and may appear within days to weeks following the surgery.

Optic neuropathy after bariatric surgery can be caused by copper, vitamin B_{12}, and thiamine deficiency. Other neuro-ophthalmic presentations are nyctalopia (the inability to see in dim light or at night) due to vitamin A or zinc deficiency and ophthalmoparesis due to vitamin E deficiency.

Muscle weakness has been reported in around 7 percent of patients after bariatric surgery, primarily in patients with hypokalemia or with global protein, vitamin D, or copper deficiencies. Postoperative rhabdomyolysis may occur and is especially frequent in patients undergoing Roux-en-Y gastric bypass; small series suggest up to three-quarters of patients may experience this complication which presents with muscle pain, typically in the gluteal region, accompanied by an increase in serum creatine kinase (CK) levels. The development of surface and deep tissue pressure during surgery may be responsible. The risk of rhabdomyolysis is greatest when the BMI of the patient is greater than $56\,\mathrm{kg/m^2}$ and the duration of the surgery is more than 230 minutes. CK testing should be performed in all patients after bariatric surgery to make an early diagnosis and promptly start fluids and diuretics. Osteomalacia and associated osteomalacic myopathy may also develop postoperatively. An acquired myotonic syndrome also has been reported.

Spinal cord dysfunction is another potential complication of bariatric surgery. Symptoms often start insidiously and may not become apparent until 5 to 10 years later. These symptoms may include gait ataxia and spasticity with pyramidal signs, paresthesias, loss of proprioception and vibratory sensation, and limb weakness often restricted to the legs. Many of these patients are found to have low serum vitamin B_{12}, vitamin E, or copper levels.

Cortical dysfunction bearing the characteristics of Wernicke encephalopathy, also known as "bariatric beriberi," complicated bariatric surgery in approximately one-quarter of patients in one study but was noted much less frequently in larger prospective investigations. Current guidelines for bariatric surgery recommend preventive thiamine supplementation (12 mg) in multivitamin treatment for all patients undergoing surgery, with higher doses for patients with suspected deficiency.[3]

Celiac Disease

Celiac disease (CD) is characterized by the constellation of diarrhea, malabsorption, weight loss, and gaseous distension that develops as a consequence of damage to the mucosa of the small intestine, triggered by an immune-mediated response to gluten. The prevalence of CD in American and European populations has been estimated to be approximately 1 percent, but because the number of undiagnosed patients may be considerable, its prevalence is probably much higher. Genetic factors play a role, and almost all patients with celiac disease possess specific variants of the HLA class II genes *HLA-DQA1* and *HLA-DQB1* that, together, encode the two chains (α and β) of the celiac-associated heterodimer proteins DQ2 and DQ8 that are expressed on the surface of antigen-presenting cells.

In recent years there has been a rise in the overall prevalence of CD in Western countries, but the reason for this "epidemic" remains unclear. The increased rate of diagnosis seems to be due to a true rise in incidence rather than merely increased awareness and detection. Approximately 30 percent of the general population carry the *HLA-DQ2/8* celiac disease susceptibility genes; however, only 2 to 5 percent of these individuals will go on to develop celiac disease, suggesting that additional environmental factors contribute to disease development. Epidemiologic, clinical, and animal studies suggest that exposure to nonpathogenic microorganisms early in life is associated with a reduced risk of developing CD. Several studies have shown an association between alteration in gut microbiota composition and function and CD, some of which can precede the onset of disease and persist when patients are on a gluten-free diet.

Individuals with classic CD have serum antigliadin antibodies along with additional gliadin-related antibodies (e.g., antiendomysial, antitransglutaminase). The pathology of CD extends beyond the GI tract, leading to proposals that the term *gluten sensitivity* be used for individuals displaying more widespread involvement, with the label CD reserved for those with evidence of enteropathy on small bowel biopsy.

Neurologic dysfunction has been reported in 6 to 12 percent of patients with CD. A systematic review reported the prevalence of neuropathy in CD patients to be up to 39 percent, with an increased risk in older and female patients.[4] In studies of CD patients with neurologic manifestations, gluten ataxia was reported in 20 to 40 percent of patients. Neurologic dysfunction in CD often is ascribed to nutritional deficiency secondary to malabsorption, although immunologic mechanisms may be an alternative explanation in some instances.

ATAXIA

Gluten ataxia has no uniquely distinguishing clinical characteristics and remains a controversial entity. Gait ataxia is present in all individuals by definition; limb ataxia, dysarthria, and ocular signs are present in most. Individuals with gluten ataxia may display cerebellar atrophy, which may be irreversible. Other neurologic symptoms may include encephalopathy, myopathy, myelopathy, and ataxia with myoclonus and chorea. Gluten ataxia usually has an insidious onset with a mean age at onset of 53 years. The classic GI symptoms of CD are present in less than 10 percent of individuals with gluten ataxia and evidence of classic CD is found on duodenal biopsy in only 25 to 33 percent. Diagnostic delays are frequent and can result in permanent neurologic disability.[4] CD patients with gluten ataxia often have oligoclonal bands in their cerebrospinal fluid, evidence of perivascular inflammation in the cerebellum, and anti-Purkinje cell antibodies. Cerebellar atrophy and white matter abnormalities may be evident on magnetic resonance imaging (MRI).

In the initial reports, antigliadin antibodies (IgG, IgA, or both) were found in 41 percent of patients with sporadic idiopathic ataxia, compared with only 15 percent of those with clinically probable multiple system atrophy (MSA), 14 percent with familial ataxia, and 12 percent of normal controls. In a follow-up study, 148 out of 635 (23%) patients with sporadic ataxia evaluated at the same clinic were noted to have evidence of gluten sensitivity.[5] Individuals with gluten ataxia, independent of intestinal involvement, demonstrate antitransglutaminase 6 IgG and IgA antibodies, whereas antitransglutaminase 2 IgA antibodies are present in persons with GI disease. The cerebellar damage has been attributed to a chronic, immune-mediated inflammatory process. Autopsy examination in several affected individuals has demonstrated Purkinje cell loss and lymphocytic infiltration within the cerebellum as well as the posterior columns of the spinal cord. Cerebellar IgA deposits containing transglutaminase 6 also have been found. Gluten ataxia sometimes responds to a gluten-free diet. Studies suggest that the presence or absence of enteropathy does not influence the beneficial response to a gluten-free diet and, therefore, patients with positive serology and negative duodenal biopsy should still be placed on a strict gluten-free diet. Intravenous immunoglobulin therapy reportedly ameliorates the ataxia in some patients.

Screening has been suggested for all individuals who present with adult-onset ataxia without any other obvious cause, but this recommendation remains controversial.

PERIPHERAL NEUROPATHY

Peripheral neuropathy accounts for around 20 percent of the neurologic abnormalities in patients with CD. Sural nerve biopsy demonstrates axonal injury in patients with chronic axonal sensorimotor neuropathy. In one study, 167 patients with CD without any symptoms of neuropathy were tested electrophysiologically. These tests did not show any evidence for subclinical neuropathy and the investigators concluded that in asymptomatic cases with celiac disease, electrophysiologic studies are not necessary. The etiology of the neuropathy is uncertain; both nutritional and autoimmune mechanisms have been proposed.

As with sporadic ataxia, some studies suggest that the prevalence of CD or of antigliadin antibodies is higher in individuals with peripheral neuropathy than in the general population. This has led to the use of the term *gluten neuropathy* for individuals with idiopathic neuropathy and serologic evidence of gluten sensitivity. Improvement with a gluten-free diet has been reported by some, but other studies have failed to demonstrate improvement.

MYOPATHY

CD is more prevalent in patients with inflammatory myopathies, particularly inclusion-body myositis. Immunologic mechanisms probably are responsible in most instances, but in one patient with CD and a myopathy resembling inclusion-body myopathy, reversal of both clinical and pathologic abnormalities was documented upon treatment with vitamin E and institution of a gluten-free diet.

EPILEPSY

An association between CD and epilepsy is controversial. The reported prevalence of epilepsy in CD has ranged from 1 to 7 percent and that of CD in individuals with epilepsy from 1 to 8 percent. A population-based study showed a moderately increased risk of epilepsy in individuals with CD. In other large studies, the presence of CD-associated antibodies did not differ between patients with epilepsy and individuals without epilepsy. A specific syndrome of epilepsy, bilateral occipital lobe calcifications, and CD has been described, largely in Italians. The mechanism for such an association is obscure. Even in CD patients without calcifications, seizures originate most frequently in the occipital lobe. A gluten-free diet may improve seizure control, especially when started early.

OTHER MANIFESTATIONS

A number of other neurologic manifestations of CD have been reported but less extensively evaluated, including migraine, sensorineural hearing loss, depression, learning disabilities, autonomic neuropathy, and neuromyelitis optica. The significance of these associations is uncertain.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a group of diseases characterized by chronic or relapsing immune activation in the GI tract resulting in inflammation. Ulcerative colitis and Crohn disease are two major forms of IBD. These two conditions share many clinical and even pathologic features, but also display important differences (Table 13-1). An autoimmune etiology in genetically susceptible individuals, characterized by a dysregulated mucosal immune response to antigens normally present within the intestinal lumen, is suspected in both.

In Europe and North America, the incidence of ulcerative colitis is in the range of 8 to 23 per 100,000 persons. Incidence rates of 6 to 23 per

TABLE 13-1 ■ Gastrointestinal Features of Inflammatory Bowel Disease

Feature	Crohn Disease	Ulcerative Colitis
Diarrhea	Common, nonbloody, less urgent	Common, bloody, urgent
Rectal bleeding	Occasional	Very common
Weight loss	Common	Uncommon
Abdominal pain	Prominent	Not prominent
Stricture formation	Common	Rare
Fistula formation	Common	Very rare

TABLE 13-2 ■ Nervous System Involvement in Inflammatory Bowel Disease

Peripheral
- Generalized
  - Sensorimotor neuropathy
    - Large fiber
    - Small fiber
  - Inflammatory demyelinating neuropathy
    - Acute
    - Chronic
- Focal
  - Mononeuropathy
  - Brachial plexopathy
- Multifocal
  - Mononeuritis multiplex
  - Multifocal motor neuropathy
  - Sensorineural hearing loss
  - Melkersson–Rosenthal syndrome

Myopathic
- Myopathy
- Myasthenia gravis
- Abscess formation

Central
- Cerebrovascular
  - Large artery
  - Lacunar
  - Venous sinus thrombosis
- Demyelinating
- Myelopathic
- Seizures
- Encephalopathy
  - Nutritional
  - Vasculitis

100,000 have been reported for Crohn disease in the same regions, but in other parts of the world, such as Asia, a previously low incidence appears to be increasing.[6]

IBD should be considered a systemic disease and involvement outside the GI tract is well described. Neurologic dysfunction appears to be relatively infrequent, with wide-ranging estimates from less than 1 to 33 percent of patients. Neurologic dysfunction may precede the appearance of GI symptoms, and both peripheral and CNS involvement occurs (Table 13-2). Autoimmune mechanisms are primarily responsible for the development of neurologic involvement in IBD; however, nutritional deficiency (vitamin B_{12} and selenium), iatrogenic (e.g., metronidazole neurotoxicity), infection, and other processes such as thromboembolic complications may secondarily involve the nervous system. Treatment for both Crohn disease and ulcerative colitis involves potent medications, including antitumor necrosis factor α (anti-TNF-α) agents, monoclonal antibodies, and immunosuppressive medications (such as cyclosporine and sulfasalazine) that can produce neurologic complications.

Peripheral Neuropathy

Peripheral neuropathy is the most frequent neurologic complication of both Crohn disease and ulcerative colitis. The reported frequency of peripheral neuropathy in IBD varies greatly among published studies, with estimates ranging from 0 to 39 percent depending on the study population characteristics and neuropathy criteria. The etiology of peripheral nerve involvement in IBD appears to be multifactorial, including nutritional deficiency, medication side effects, and an autoimmune mechanism as part of the primary disease. The phenotype of peripheral neuropathy in IBD is diverse, but peripheral neuropathy is usually more severe in patients with Crohn disease than in patients with ulcerative colitis. Involvement may take the form of focal (e.g., mononeuropathy, cranial neuropathy, brachial plexopathy), multifocal (e.g., mononeuritis multiplex, multifocal motor neuropathy), and generalized (acute or chronic inflammatory demyelinating polyneuropathy, small- or large-fiber axonal sensorimotor neuropathy) neuropathic processes. However, it also frequently includes ataxic and demyelinating forms.

Peripheral neuropathy occurs late in the course of the disease and mainly during periods of bowel disease inactivity. The common phenotypes of peripheral neuropathy are a mild, chronic, large-fiber, sensory-predominant polyneuropathy and a moderately severe immune radiculoplexus neuropathy. Carpal tunnel syndrome appears to be the most frequently occurring isolated mononeuropathy in IBD. Axonal neuropathy occurs more frequently than demyelinating neuropathy.

Two specific patterns of cranial nerve involvement have been described in IBD. Acute sensorineural hearing loss or chronic subclinical hearing impairment has been described in ulcerative colitis. In contrast, Melkersson–Rosenthal syndrome, characterized by recurrent facial nerve palsy along with intermittent orofacial swelling and fissuring of the tongue, has been reported in patients with Crohn disease.

DEMYELINATING DISEASE

An association between IBD, especially ulcerative colitis, and multiple sclerosis (MS) has been reported. In a systematic review, it was suggested that both IBD and MS patients have a 50 percent increased risk of MS or IBD comorbidity, respectively, with no apparent difference between patients with Crohn disease or ulcerative colitis.[7] The odds ratio for MS in patients with IBD is around 1.5. White matter lesions may be present on MRI in patients with IBD; whether these represent MS or another ischemic or demyelinating process is unclear. The development of demyelination within the CNS as an adverse effect of anti-TNF-α agents has been reported.

CEREBROVASCULAR DISEASE

Vascular complications are rare, but well-documented, extraintestinal manifestations of IBD. A large population-based case-control study demonstrated an increased risk of ischemic stroke only in younger individuals (age <50 years) with Crohn disease. It is estimated that 1 to 6 percent of adults with IBD and 3 percent of children with IBD develop cerebrovascular complications at some point during the course of their disease. Responses to both immunosuppressive therapy (e.g., corticosteroids and azathioprine) and anticoagulation have been reported, suggesting that both hypercoagulable and autoimmune processes may play a role.

A variety of cerebrovascular events has been reported in Crohn disease and ulcerative colitis, including both large-artery and lacunar infarcts. Cerebral venous sinus thrombosis in IBD occurs more frequently in ulcerative colitis; individuals with active disease are at greater risk. Thrombocytosis due to enhanced platelet aggregation and platelet activation in patients with IBD can cause stroke. Once activated, platelets release inflammatory mediators and increase the likelihood of cerebral venous sinus or arterial thrombosis. The lateral and superior sagittal sinuses are involved most frequently. Severe iron-deficiency anemia may be a significant risk factor for thrombosis.

MYOPATHY

Myopathy is relatively rare in IBD, occurring in 0.5 percent of patients. Symptoms may precede the appearance of GI dysfunction, but this is unusual.

Both generalized inflammatory muscle disease and focal muscle involvement have been described, primarily in Crohn disease. Abscess formation in the psoas or other muscles is an important potential complication; psoas muscle abscess is characterized by flank, pelvic, or abdominal pain, usually associated with fever and leukocytosis. The diagnosis is confirmed by ultrasound or computerized tomography (CT). Focal myositis involving the gastrocnemius and other muscles has been reported.

MYELOPATHY

A slowly progressive myelopathy may develop in the setting of IBD and may account for approximately 25 percent of patients with neurologic involvement. It is more likely to occur in patients with Crohn disease, who may develop vitamin B_{12} deficiency as a consequence of surgical resection of the terminal ileum. Patients with Crohn disease also may develop a more acute myelopathy or cauda equina syndrome due to empyema from extension of a fistula to the epidural or subdural space.

OTHER MANIFESTATIONS

Seizures may occur as a complication of the surgical management of IBD, precipitated by fluid overload, electrolyte imbalance, hypoxia, and corticosteroid administration or withdrawal. They may occur also as a complication of cyclosporine treatment.

In one prospective multicenter study in patients with Crohn disease, the incidence of restless legs syndrome (RLS) was 43 percent and prevalence was 30 percent. In this population, symptoms of RLS started during or after the onset of Crohn disease symptoms in most patients, suggesting a link between these disorders.[8]

Diffuse encephalopathy and acute disseminated encephalomyelitis also have been reported. Both Wernicke encephalopathy and possible selenium-induced encephalopathy have been described in individuals with Crohn disease receiving total parenteral nutrition. Autonomic neuropathy has been reported rarely in both Crohn disease and ulcerative colitis. Both ocular and generalized forms of myasthenia gravis (MG) have been reported with both disorders. Case reports of patients with MG and IBD describe improvement of symptoms following surgical interventions (one with thymectomy and one with protocolectomy), suggesting an immunologic link between MG and IBD.

Whipple Disease

Although originally described as a GI disease, with symptoms of diarrhea, weight loss, and abdominal pain, Whipple disease is a multisystem disorder that also may be characterized by joint, dermatologic, lymphatic, cardiac, pulmonary, ocular, and neurologic dysfunction. The average age of symptom onset is approximately 50 years, and males are affected much more frequently than females. Over two-thirds of patients are either farmers or have occupational exposure to soil. This disease was initially thought to be related to an uncultured bacteria, but DNA sequencing has demonstrated *Tropheryma whipplei* to be responsible.

Neurologic dysfunction is the presenting feature in approximately 5 percent of persons with Whipple disease. Symptoms of CNS involvement eventually develop in 10 to 40 percent of patients, and postmortem examinations demonstrate CNS lesions in over 90 percent of individuals (Table 13-3). Cognitive impairment, such as dementia, is the most frequently observed neurologic manifestation, occurring in around 70 percent of patients, often accompanied by psychiatric symptoms such as depression and personality or behavioral changes. Peripheral neuropathy is very rare in Whipple disease and usually is due to micronutrient or vitamin deficiency caused by malabsorption. Cerebellar dysfunction with gait and balance impairment occurs in approximately 20 percent of persons; pyramidal tract abnormalities also may occur. Symptoms indicative of hypothalamic involvement, such as insomnia, hypersomnia, hyperphagia, polyuria, and polydipsia, are uncommon. Myopathy has been reported in a small number of patients; in these cases muscle biopsy shows muscle fiber atrophy and intrafascicular macrophages which are PCR positive for *Tropheryma whipplei*.

TABLE 13-3 ■ Neurologic Features of Whipple Disease

- Cognitive impairment
- Psychiatric dysfunction
  - Depression
  - Personality change
- Hypothalamic manifestations
  - Insomnia
  - Hypersomnia
  - Hyperphagia
  - Polydipsia and polyuria
- Oculomasticatory myorhythmia
- Oculofacial-skeletal myorhythmia
- Vertical gaze impairment
- Seizures
- Ataxia
- Peripheral neuropathy

Oculomasticatory myorhythmia, characterized by the combination of pendular convergence nystagmus and concurrent slow, rhythmic synchronous contractions of the masticatory muscles, develops in approximately 20 percent of individuals with CNS manifestations of Whipple disease. These movements invariably are accompanied by a supranuclear vertical gaze paresis. Sometimes the muscle contractions also involve the extremities, prompting use of the term oculofacial-skeletal myorhythmia. These two movement disorders are considered by some to be pathognomonic of Whipple disease. Other ophthalmologic abnormalities, such as ptosis, internuclear ophthalmoplegia, and pupillary dysfunction, also may occur. Whipple disease can present without its classic manifestations, but with prominent parkinsonism and with slowing and curved trajectory of vertical saccades.

Prompt diagnosis of Whipple disease is important because effective treatment is available. Cerebrospinal fluid (CSF) PCR analysis appears to be a more sensitive method of diagnosis than identification of PAS-positive inclusions in macrophages in duodenal biopsy specimens, but there is some evidence that *Tropheryma whipplei* DNA may be present in healthy individuals without the disorder. In individuals with CNS symptomatology, brain biopsy is positive in 80 percent of instances. CSF analysis may show an inflammatory response that sometimes contains PAS-positive macrophages. CSF PCR is positive in 80 percent of patients with Whipple disease and neurologic symptoms.

The rarity of the disorder has precluded formal clinical trials, but an initial 2-week course of parenteral therapy with either a combination of penicillin G and streptomycin or with a third-generation cephalosporin (e.g., ceftriaxone) is recommended, followed by a 1-year course of oral trimethoprim-sulfamethoxazole.[9] The prolonged course of trimethoprim-sulfamethoxazole, which crosses the blood–brain barrier, is intended to treat CNS involvement. A combination of doxycycline and hydroxychloroquine, supplemented by sulfadiazine, is an alternative regimen. It is important to treat the disease adequately when first identified, because CNS relapses have a poor prognosis and high mortality rate.

Malabsorption Syndromes

Historically, maldigestion is defined as defective breakdown of nutrients, and malabsorption is defined as defective mucosal absorption. However, the digestive process is more complex and factors such as solubilization, intestinal motility, and hormone secretion contribute to the normal absorption of nutrients, vitamins, and minerals. Malabsorption can be caused by many diseases of the small intestine and also by diseases of the pancreas, liver, biliary tract, and the stomach. Abdominal distension and pain, flatulence, diarrhea, weight loss, and ascites are the classic GI features of malabsorption. Systemic involvement may be characterized by dermatologic, musculoskeletal, renal, hematologic, reproductive, and neurologic dysfunction. These and other nutritional disorders are discussed further in Chapter 15.

VITAMIN E DEFICIENCY

Neurologic dysfunction in the setting of vitamin E deficiency can be genetic in origin, due to a mutation in the α-tocopherol transfer protein gene, with a clinical presentation that can mimic Friedreich ataxia. In most instances, however, it is the consequence of fat malabsorption, which can occur in a variety of circumstances.

Neurologic symptoms and signs of vitamin E deficiency may include ataxia, dysarthria, and nystagmus. Symptoms and signs of peripheral neuropathy, including paresthesias, impaired proprioception and vibration, and hyporeflexia are common. Proximal muscle weakness from myopathy, pigmentary retinopathy, action tremor, limb dysmetria, and dystonia also have been described.

Somatosensory evoked potentials may demonstrate abnormalities indicative of posterior column dysfunction. Diffuse white matter changes have been described in patients with vitamin E deficiency, in both the cerebrum and spinal cord; some of these patients present with upper motor neuron signs.

The appearance of symptoms of vitamin E deficiency can be strikingly delayed. In post-gastrectomy patients, it may take up to 50 months for evidence of vitamin E deficiency to appear. Vitamin E supplementation in high doses (800 mg daily) helps to prevent progression and may even reverse some of the neurologic signs.

FAMILIAL HYPOCHOLESTEROLEMIA

Three distinct genetic disorders—familial hypobetalipoproteinemia, abetalipoproteinemia, and chylomicron retention disease—have been identified as causes of chronic diarrhea, malabsorption, malnutrition, growth retardation, and vitamin E deficiency. Of the three, neurologists are most familiar with abetalipoproteinemia, previously known as Bassen–Kornzweig syndrome.

Abetalipoproteinemia is an autosomal recessive disorder due to a mutation in the microsomal triglyceride transfer protein (*MTP*) gene on chromosome 4, which leads to impaired biogenesis of chylomicrons and very-low-density lipoprotein (VLDL) along with an inability to absorb fats and fat-soluble vitamins including vitamin E. The clinical features of abetalipoproteinemia include steatorrhea, diarrhea, retinitis pigmentosa, acanthocytosis, and a variety of neurologic features. Blood lipid analysis demonstrates extremely low plasma levels of total cholesterol, VLDL, and low-density lipoproteins (LDL); apolipoprotein B, triglycerides, and chylomicrons are virtually absent. GI symptoms usually are evident during infancy, but neurologic dysfunction may not appear until individuals are in their teens or even older. Neurologic symptoms include progressive cerebellar ataxia and sometimes a sensorimotor neuropathy. Both the ataxia and the peripheral neuropathy probably are due to vitamin E deficiency. Additional neurologic abnormalities that have been described include upper motor neuron signs and both resting and postural tremor. Treatment of neurologic dysfunction with both vitamin E and vitamin A has been advocated, but results have been mixed.

TROPICAL SPRUE

Tropical sprue remains a significant cause of malabsorption in both indigenous residents of tropical countries and travelers visiting the tropics. The etiology remains obscure but possibly is the consequence of small intestinal mucosal damage inflicted by protozoa, helminths, bacteria, viruses, or a variety of other disease processes of inflammatory, autoimmune, or neoplastic origin. Diagnosis requires the demonstration of malabsorption and the exclusion of other specific pathologies including celiac disease, chronic pancreatitis, and parasitic infections.

Infrequently encountered in North America, tropical sprue has been reported to account for approximately 40 percent of malabsorption in children and adults in some portions of south Asia. The usual presentation includes chronic diarrhea, steatorrhea, glossitis, abdominal distention, and weight loss. Tropical sprue typically involves the entire length of the small intestine, in contrast to celiac disease, which usually spares the terminal ileum. Mucosal damage results in malabsorption of fat, carbohydrates, and multiple vitamins, including folate and vitamins A, E, and B_{12}.

Neurologic symptoms are present in approximately two-thirds of individuals with tropical sprue. Proximal muscle weakness and peripheral neuropathy are most common. Night blindness, presumably due to vitamin A deficiency, and combined system degeneration, presumably the result of vitamin B_{12} deficiency, have been described. The peripheral neuropathy has been attributed to vitamin E deficiency.

Antibiotic therapy, typically with tetracycline or doxycycline for 6 months, and a high-calorie, high-protein, fat-restricted diet are the standard treatments for tropical sprue, but abnormal small intestine permeability may remain following treatment.

WERNICKE ENCEPHALOPATHY

Wernicke encephalopathy (WE) is an acute neuropsychiatric syndrome that is most closely linked to chronic alcoholism with nutritional thiamine deficiency, but also can result from malabsorption of thiamine (see Chapters 15 and 33). In nonalcoholic patients, the full classic triad of neurologic features—mental status changes, ophthalmoplegia, and ataxia—develops in only 10 to 16 percent of individuals.

Thiamine is absorbed primarily in the duodenum, but the stomach also plays a role. As a result, Wernicke encephalopathy has been documented following bariatric surgery. Oudman and colleagues reviewed all published cases after bariatric surgery between 1985 and 2017 and reported that the latency between bariatric surgery and onset of symptoms was not significantly different between the three most reported surgical procedures (gastroplasty, gastric bypass, and sleeve gastrectomy).[3] Wernicke encephalopathy developed as early as the first month and as late as the 425th month after surgery. Although a large majority of cases (79.1%) developed in the first 6 months, 4 to 12 weeks postoperatively was the most frequent time frame. Gastric bypass or a restrictive procedure is the most common operation that predisposes to it. Repeated vomiting, presumably with decreased thiamine absorption as a result, is a frequent risk factor. Individuals undergoing Roux-en-Y gastric bypass have an additional risk since thiamine is predominantly absorbed in the duodenum, which is bypassed following this procedure.

Werrnicke encephalopathy also has been described in individuals with other causes of malabsorption. In one patient with a history of neonatal necrotizing enterocolitis and subsequent bowel resection, it developed as an adult during pregnancy and was attributed to long-standing chronic malabsorption exacerbated by the pregnancy.

PELLAGRA

Pellagra often is considered to be extinct in developed countries, but it still occurs in rare instances. It is caused by niacin deficiency, but can also develop secondary to deficiency of tryptophan, a precursor of niacin. Pellagra most often is diagnosed in individuals with chronic alcoholism and inadequate nutritional intake, but also may develop in patients with HIV infection, anorexia, and malabsorption syndromes.

The classic clinical features of pellagra include the triad of dermatitis, diarrhea, and dementia, although most individuals do not have all three features. In addition to dementia, neurologic abnormalities may include headache, irritability, poor concentration, apathy and confusion, vertigo, myoclonus, tremor, rigidity, weakness, dysphagia, seizures, and various psychiatric symptoms. As pellagra advances, patients first become disoriented, confused, and delirious, then become stuporous and comatose, and finally die.

Pellagra may develop in persons with Crohn disease as a consequence of niacin deficiency due to malabsorption and tryptophan wastage with increased urinary excretion of 5-hydroxyindoleacetic acid. Pellagra has been reported in infectious colitis and with intestinal bacterial overgrowth resulting in malabsorption.

Copper Deficiency

Copper deficiency is best recognized in Menkes disease, in which there is a genetically based inability to transport copper across the intestinal barrier due to a mutation in the *ATP7A* gene. However, impairment of intestinal copper absorption also may occur in the setting of various acquired malabsorptive processes.

Copper is absorbed in the proximal small intestine, primarily in the duodenum but also to a lesser extent in the stomach and more distal small intestine. Processes that remove or impair these absorptive sites may result in eventual copper deficiency; thus, copper malabsorption has been identified in individuals who have previously undergone gastric or intestinal surgery. Although malabsorption is the most frequent cause, copper deficiency also may follow excessive zinc ingestion.

The clinical features of copper deficiency myelopathy closely mimic those of subacute combined degeneration due to vitamin B_{12} deficiency. The combination of posterior column dysfunction with sensory ataxia and associated corticospinal tract abnormalities is common to both; peripheral neuropathy also may be present, although it is not as common in copper deficiency as it is with vitamin B_{12} deficiency. Hematologic manifestations frequently are present in both; anemia and neutropenia are characteristic in copper deficiency and the anemia may be microcytic, macrocytic, or normocytic. Optic neuropathy also may be present. T2 hyperintensities within the dorsal columns of the cervical spinal cord may be seen on MRI in both copper deficiency myelopathy and vitamin B_{12} deficiency.

The response to copper replacement therapy is inconsistent. Although the hematologic abnormalities typically respond fully over the course of 4 to 12 weeks of therapy, neurologic dysfunction may only be partially reversible. In a retrospective study in which 16 copper-deficient patients were followed for 5 years, 93 percent of hematologic abnormalities resolved with copper supplementation, but only 25 percent of neurologic symptoms improved.[10]

HEPATIC DISORDERS

When hepatic disease, regardless of its cause, progresses to a point that the liver becomes incapable of effectively eliminating toxic substances, neurologic dysfunction can ensue as these toxins, notably ammonia, cross the blood–brain barrier. Hepatic failure most often evolves slowly, over a period of many months. However, in acute liver failure, erupting over a period of days to weeks, neurologic symptoms often predominate. The cerebral dysfunction that is due to liver insufficiency or portosystemic shunting is discussed in Chapter 12.

The most widely recognized neurologic complications of serious hepatocellular failure include hepatic encephalopathy, diffuse cerebral edema, Wilson disease, hepatic myelopathy, acquired hepatocerebral degeneration, cirrhosis-related parkinsonism, and osmotic demyelination syndrome. A predominantly axonal, length-dependent peripheral neuropathy may occur in patients with chronic liver disease. It is often subclinical or oligosymptomatic, but distal sensory loss and areflexia are sometimes found on examination, and quantitative studies may reveal abnormalities of small-fiber function. Median neuropathy at the wrist (carpal tunnel syndrome) is common. Autonomic neuropathy also is frequent, regardless of whether there is a concomitant somatic neuropathy, and tends to involve parasympathetic (vagal) more often than sympathetic components; its severity relates to the severity, but not the cause, of the hepatic dysfunction. The presence of vagal dysfunction in patients with well-compensated chronic liver disease indicates a substantially worse prognosis for survival.

Various disorders causing hepatic dysfunction—such as alcohol-induced cirrhosis, porphyria, polyarteritis nodosa, and primary biliary cirrhosis—may independently cause peripheral nerve dysfunction.

However, because the severity of neuropathy correlates with that of the liver disease regardless of its etiology, it seems likely that the peripheral neuropathy is caused by hepatocellular damage.

Patients infected with hepatitis C virus may develop various neuromuscular complications. A fulminant vasculitic syndrome and progressive mononeuropathy multiplex may occur in those with cryoglobulinemia, but a length-dependent oligosymptomatic distal peripheral neuropathy may occur without cryoglobulinemia. Acute or chronic demyelinating neuropathies have been reported in the setting of viral hepatitis. Muscle disease also occurs. Myalgia is common but of uncertain cause; muscle weakness is uncommon. There have been several case reports of polymyositis or dermatomyositis occurring in patients with hepatitis C. In addition, interferon therapy for hepatitis C infection may precipitate or aggravate the myopathy.

Patients with primary biliary cirrhosis form a separate group in which a pure sensory neuropathy may develop, with or without xanthomatous infiltration of the nerves. Autonomic involvement also may occur.

Wilson Disease

Wilson disease is an autosomal recessive disorder caused by a mutation in the *ATB7P* gene on chromosome 13. More than 700 mutations have been identified, and most affected patients are compound heterozygotes.[11] The prevalence rate most often has been quoted as between 1:30,000 and 1:40,000, although recent studies suggest that this may be an underestimate. Missense and nonsense *ATP7B* mutations have been most frequently identified, followed by insertions/deletions and splice site and point mutations; exonic mutations causing exon skipping also have been identified.[12]

PATHOPHYSIOLOGY

The defective ATP7B protein cannot carry out its transport functions within the hepatocyte. As a result, copper is neither delivered for ceruloplasmin formation nor transported into the bile canaliculus for excretion. The defect in biliary excretion of copper results in a slow accumulation of copper within the liver. Eventually, the ability of the liver to store the copper is exceeded and unbound copper escapes from the liver and accumulates in other sites, including the nervous system.

CLINICAL PRESENTATION

Hepatic Manifestations

Approximately 40 to 50 percent of patients with Wilson disease experience hepatic symptoms as their initial manifestation. These individuals tend to present at an earlier age (average 11.4 to 15.5 years) than those with a primary neurologic or psychiatric presentation. Onset of symptoms before age 6 is rare; presentation with hepatic dysfunction has been reported as late as age 74.

The most frequent hepatic presentation is that of slowly progressive liver failure with cirrhosis, ascites, esophageal varices, and splenomegaly. A clinical picture similar to autoimmune (chronic active) hepatitis is evident in 10 to 30 percent; acute fulminant hepatic failure occurs in approximately 5 percent. The pattern of liver enzyme abnormalities in the setting of fulminant hepatic failure may provide clues to the diagnosis as hemolysis may produce disproportionate elevation of the total bilirubin. The combination of an alkaline phosphatase to total bilirubin ratio of less than 4 and an aspartate aminotransferase to alanine aminotransferase ratio of greater than 2.2 is highly suggestive of Wilson disease, especially if the serum hemoglobin level also is reduced.

Neurologic Manifestations

Neurologic dysfunction is the second most frequent initial clinical manifestation of Wilson disease, with estimates that range from 35 to 60 percent. The average age of symptom onset (around 20 years) is later than when the initial presentation is hepatic in nature, but ages from 6 to 72 years have been reported.

Tremor is the initial symptom of neurologic involvement in around one-half of patients. The tremor typically is asymmetric and may be resting, postural, kinetic, or a combination of these. Dystonia may be as frequent as tremor. Chorea occurs relatively infrequently, but may be present at the time of diagnosis in around 15 percent of patients. Athetosis also has been described. Parkinsonism frequently is present, with one case series finding 45 percent of patients with neurologic dysfunction having parkinsonian symptoms or signs. Although unusual, myoclonus also has been reported.

Cerebellar dysfunction develops in 25 to 50 percent of individuals. It may take the form of ataxia, dysarthria, kinetic tremor, or incoordination. Dysarthria in one study was evident in 91 percent of patients at diagnosis. Several patterns of dysarthria have been described including a hypokinetic form with difficulty in initiating speech, reduced volume, phonation, and intonation; inadequate tongue movements; and imprecise articulation along with a tendency for speech to accelerate as it proceeds. Dysarthria of cerebellar or brainstem origin also has been described. Dysphagia may develop during the course of the illness. An unusual laugh, in which most of the sound is generated during inspiration, also may occur.

Gait abnormalities are another common neurologic feature, present in 45 to 75 percent of patients at diagnosis. Gait impairment ranges from parkinsonian, with small shuffling steps and difficulty initiating gait, to cerebellar, with a wide-based and unsteady appearance.

Sleep disorders also may occur. Insomnia, restless legs syndrome, cataplexy, daytime sleepiness, and REM sleep behavior disorder all have been described; the latter two may precede the actual diagnosis.[13]

Psychiatric Manifestations

Psychiatric symptoms are the presenting feature in approximately 15 to 20 percent of patients with Wilson disease and may result in delays in diagnosis. Most individuals will experience psychiatric dysfunction at some point during their illness. This may range from subtle personality changes to mania and frank psychosis. Major depression develops in around one-quarter of patients. Suicidal behavior has been described in some.

Ophthalmologic Manifestations

The ophthalmologic hallmark of the disease is the formation of Kayser–Fleischer rings within the cornea (Fig. 13-1). They are virtually always bilateral, but unilateral Kayser–Fleischer rings have been described, possibly as a consequence of reduced intraocular pressure in the eye without the ring. Because of their dark color, Kayser–Fleischer rings often can be identified easily in patients with blue eyes, but only with difficulty in brown-eyed persons without the benefit of slit-lamp examination. Kayser–Fleischer rings first appear in the superior aspect of the cornea, followed by the inferior aspect; the medial and lateral portions of the ring then subsequently fill in. Because of this pattern of ring evolution, it is important to lift the eyelid during the examination so that incomplete ring formation is not overlooked.

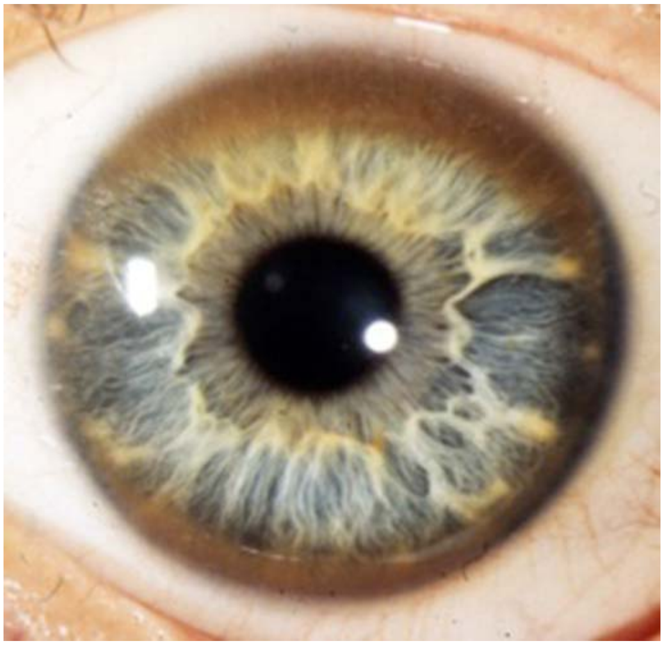

FIGURE 13-1 ■ Kayser–Fleischer ring. (Courtesy of Wayne Cornblath, MD, University of Michigan, Kellogg Eye Center, Ann Arbor, Michigan.)

Kayser–Fleischer rings virtually always are present in patients with neurologic or psychiatric symptoms, but they may not yet have formed in persons who present with isolated hepatic involvement.

Other Manifestations

Radiographic evidence of osteoporosis is common. Coombs-negative hemolytic anemia may present initially in 10 to 15 percent of cases. Renal impairment is the initial symptom in nearly 10 percent of children in some studies. Myocardial involvement in Wilson disease, presumably due to copper deposition within the heart, is underrecognized. Autonomic dysfunction, most often asymptomatic and evident only upon neurophysiologic testing, has been noted in almost 40 percent of persons, predominantly those with neurologic involvement. Skin changes, including hyperpigmentation of the legs and a dark complexion, may occur and be mistaken for Addison disease. Bluish discoloration of the lunulae of the nails and acanthosis nigricans also have been reported.

DIAGNOSIS

The presence of over 700 different mutations has made genetic testing difficult. However, it has been suggested that *ATP7B* gene sequencing should now be standard practice in the diagnosis of Wilson disease.

Determination of hepatic copper content via liver biopsy is currently the single most sensitive and specific test for the diagnosis. Hepatic copper elevation is typically quite striking, with levels greater than 250 μg/g dry tissue, compared with normal values of 15 to 55 μg/g. In patients with neurologic or psychiatric dysfunction, liver biopsy is generally unnecessary since other tests will provide the diagnosis; it is, however, usually required in individuals presenting with hepatic dysfunction.

The visualization of Kayser—Fleischer rings is an invaluable aid in diagnosis. Slit-lamp examination by a neuroophthalmologist or experienced ophthalmologist should be part of the diagnostic evaluation, particularly in persons displaying neurologic or psychiatric dysfunction. Individuals with only hepatic dysfunction may not display Kayser—Fleischer rings because copper accumulation may not yet have exceeded the liver's capacity to store the excess. Anterior segment optical coherence tomography (AS-OCT) may offer improved objectivity and accuracy over slit-lamp examination in identifying Kayser—Fleischer rings.[14]

Serum ceruloplasmin determination cannot be relied upon as the sole screening study in patients with possible Wilson disease. Ceruloplasmin may be normal or only slightly lower than normal in 5 to 15 percent of persons with the disease. Since ceruloplasmin is an acute-phase reactant, it may increase and reach normal levels during pregnancy, with estrogen or steroid administration, in the setting of infections, or with various inflammatory processes including hepatitis. As many as 10 to 20 percent of heterozygotes for Wilson disease have subnormal ceruloplasmin levels.

A 24-hour urinary copper determination is generally considered to be the single best screening test in symptomatic patients, although a recent analysis suggests that measuring copper in the first morning urine may be just as accurate and much easier to reliably collect.[15] Urinary copper levels in symptomatic patients typically exceed 100 μg/day. However, in individuals who are asymptomatic, 24-hour urinary copper excretion may be within the normal range because the ability of the liver to store the accumulating copper has not yet been exceeded.

Although serum copper levels, which measure total serum copper, are characteristically low in patients with Wilson disease, they are of little diagnostic value. Total serum copper largely reflects ceruloplasmin concentrations and is low simply because of the marked reduction in ceruloplasmin. In a patient with fulminant hepatic failure, however, serum copper levels become markedly elevated due to the sudden release of copper from tissue stores.

A variety of neuroimaging changes may occur. The most characteristic brain MRI changes include the presence of increased signal intensity in the basal ganglia on T2-weighted sequences and reduced signal intensity on T1-weighted sequences. The T2 sequence has a higher sensitivity than the T1 and FLAIR sequences in detecting brain lesions in Wilson disease. Several distinctive neuroimaging abnormalities, such as the "face of the giant panda" sign in the midbrain, the "face of the miniature panda" sign in the pons, and the "bright claustrum sign," have been described, but they are present in only a relatively small percentage of patients, limiting their diagnostic utility.

Measurement of the incorporation of radioactive copper (^{64}Cu) into ceruloplasmin also has been employed for diagnostic evaluation. However, difficulty obtaining the radioactive isotope limits its availability, and an overlap of values between individuals with Wilson disease and heterozygous carriers limits the procedure's specificity.

CSF copper levels are elevated in persons with neurologic dysfunction and decline with successful symptomatic treatment, but measurement is not performed in routine clinical practice.

TREATMENT

Dietary restriction of copper has, in general, not been a successful treatment approach. When administered orally, zinc is absorbed by intestinal enterocytes and induces metallothionein formation, which then binds both zinc and copper and inhibits their intestinal absorption. The use of zinc as "maintenance" therapy following initial treatment of neurologically symptomatic individuals with other, more potent, decoppering agents has become common.

Some investigators now even consider zinc to be first-line therapy. Zinc generally is well tolerated, with very little toxicity.

Penicillamine avidly chelates copper and holds it until the complexed copper is excreted in the urine. Improvement in function following initiation of penicillamine therapy typically does not become evident for 2 to 3 months, and then may extend gradually over 1 to 2 years. Acute sensitivity reactions and a variety of other potential adverse effects may complicate chronic penicillamine therapy. Penicillamine has the propensity to produce an initial deterioration in neurologic function when initiated, perhaps in as many as 50 percent of patients. The risk that penicillamine might induce irreversible neurologic deterioration following its initiation has led to a divergence in opinion as to the proper role of the drug in treatment. Some authors suggest continuing to use penicillamine but with low initial doses; others recommend treatment induction with other, ostensibly safer, medications.

Trientine is a copper-chelating agent with a mechanism of action similar to that of penicillamine but with a somewhat gentler decoppering effect that may make it less prone to trigger deterioration in neurologic function. Adverse effects from trientine are less frequent than with penicillamine.

Tetrathiomolybdate remains an experimental treatment modality, unavailable for general use. It has a distinct, dual mechanism of action that separates it from other available treatment modalities. It functions both to inhibit copper absorption from the GI tract and to complex with copper in the bloodstream, reducing the copper load both systemically and in the gut lumen.

Deep brain stimulation (DBS) targeting the posterior subthalamic area has been reported to improve both tremor and dystonia in Wilson disease, but further work is still needed to confirm this benefit.

Orthotopic liver transplantation is essentially the one effective treatment for fulminant hepatic failure in Wilson disease. Its potential utility in treating the patient with stable liver function but severe, progressive neurologic abnormalities despite optimal medical management has been considered but is not routine standard of care.

In an individual who is asymptomatic, therapy should be initiated with zinc alone. In a patient with hepatic but not neurologic or psychiatric dysfunction, introduction of both a chelating agent and zinc simultaneously may be ideal. Trientine has gained favor over penicillamine in recent years. Some might opt for zinc monotherapy in this setting.

No unequivocally clear consensus has yet developed for treating patients with established neurologic or psychiatric dysfunction. The primary choice is whether to initiate therapy with penicillamine or trientine. Both have their advocates, but a growing preference for trientine seems evident. Zinc is usually reserved for maintenance therapy following initial employment of a chelating agent.

Guidelines for the diagnosis and treatment of Wilson disease have been published by the European Association for the Study of the Liver (EASL).

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CHAPTER

14

Disturbances of Gastrointestinal Motility and the Nervous System

MICHAEL CAMILLERI

INTERACTIONS BETWEEN THE EXTRINSIC NERVOUS SYSTEM AND THE GUT
- Enteric and Extrinsic Nervous Supply to the Digestive Tract
- The Layers of the Gut

COMMON GASTROINTESTINAL SYMPTOMS IN NEUROLOGIC DISORDERS
- Dysphagia
- Gastroparesis
- Chronic Intestinal Pseudo-Obstruction
- Constipation
- Diarrhea
- Fecal Incontinence

EXTRINSIC NEUROLOGIC DISORDERS CAUSING GUT DYSMOTILITY
- Brain Diseases
  - *Stroke*
  - *Alzheimer Disease*
  - *Parkinsonism*
  - *Head Injury*
  - *Autonomic Epilepsy and Migraine*
  - *Amyotrophic Lateral Sclerosis*
  - *Postpolio Dysphagia*
  - *Brainstem Lesions*
- Autonomic System Degenerations
  - *Pandysautonomias or Selective Dysautonomias*
  - *Idiopathic Orthostatic Hypotension*
  - *Postural Orthostatic Tachycardia Syndrome*
  - *Multiple System Atrophy*
- Spinal Cord Lesions
  - *Spinal Cord Injury*
  - *Multiple Sclerosis*
  - *Neuromyelitis Optica*
- Peripheral Neuropathy
  - *Acute Peripheral Neuropathy*
  - *Chronic Peripheral Neuropathy*

GENERAL MUSCLE DISEASES CAUSING GUT DYSMOTILITY

IDENTIFICATION OF EXTRINSIC NEUROLOGIC DISEASE WITH GASTROINTESTINAL SYMPTOMS OF DYSMOTILITY

MANAGEMENT OF GASTROINTESTINAL MOTILITY DISORDERS

CONCLUDING COMMENTS

INTERACTIONS BETWEEN THE EXTRINSIC NERVOUS SYSTEM AND THE GUT

The major functions of the gastrointestinal tract (motor, fluid and electrolyte transport, secretory, storage, and excretory functions) result from an intricately balanced series of control mechanisms (Fig. 14-1): the electrical and contractile properties of the smooth muscle cell that result from transmembrane fluxes of ions. Control is by the enteric nervous system through chemical transmitters such as acetylcholine, biogenic amines such as serotonin, neuropeptides released within the gut, and nitric oxide. These transmitters may act as circulating hormones or at the site of release (paracrine or neurocrine function). Regulation by extrinsic pathways (sympathetic and parasympathetic nervous systems) modifies the functions that are intrinsically controlled by the enteric mechanisms. Disorders of the nervous system affecting gastrointestinal tract function are manifested primarily as abnormalities in motor (rather than sensory, absorptive, or secretory) functions of the gut.

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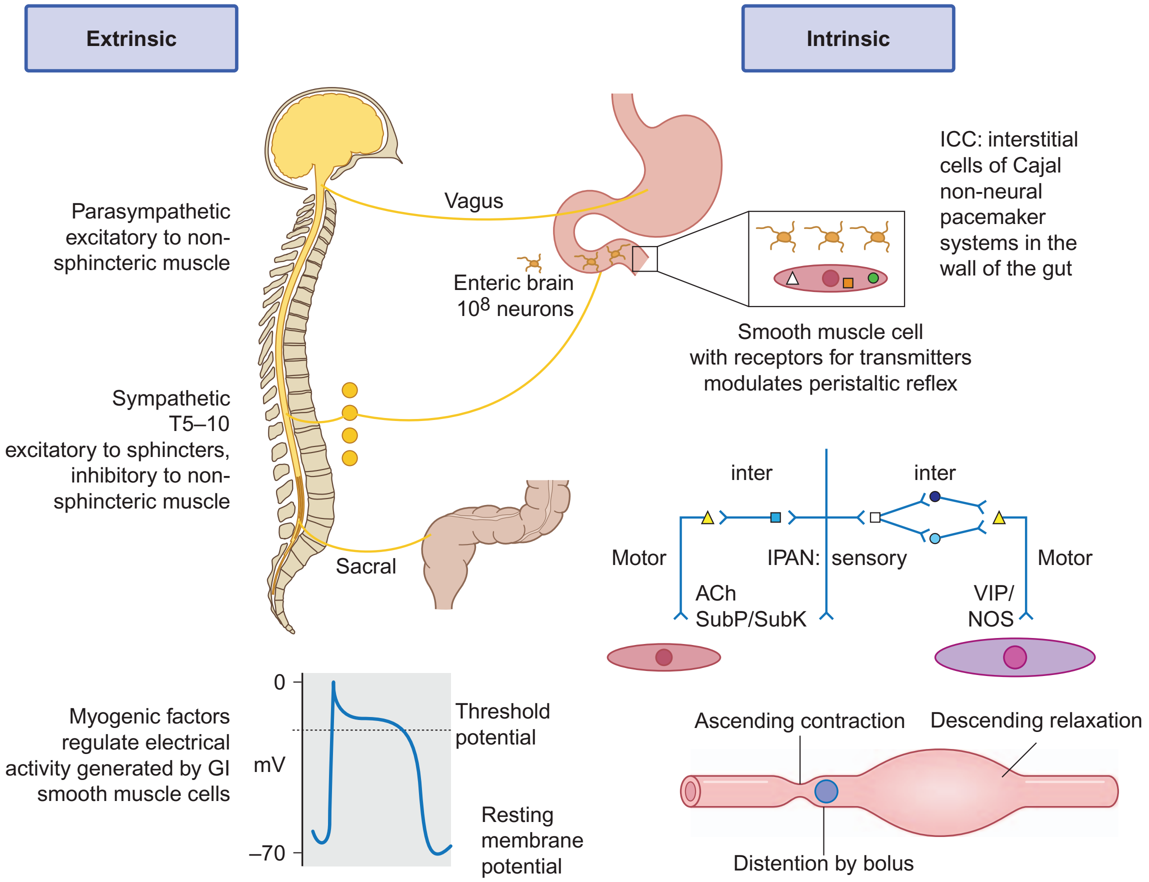
Extrinsic
Intrinsic
Parasympathetic excitatory to non-sphincteric muscle
Vagus
Enteric brain
10^8 neurons
ICC: interstitial cells of Cajal non-neural pacemaker systems in the wall of the gut
Smooth muscle cell with receptors for transmitters modulates peristaltic reflex
Sympathetic T5–10 excitatory to sphincters, inhibitory to non-sphincteric muscle
inter
inter
Motor
IPAN: sensory
Motor
ACh
SubP/SubK
VIP/
NOS
Sacral
Myogenic factors regulate electrical activity generated by GI smooth muscle cells
0
mV
–70
Threshold potential
Resting membrane potential
Ascending contraction
Descending relaxation
Distention by bolus

FIGURE 14-1 ■ Control of gut motility: interactions between extrinsic neural pathways and the intrinsic nervous system ("enteric brain" or enteric nervous system plexuses) modulate contractions of gastrointestinal smooth muscle. Interactions between transmitters (e.g., peptides and amines) and receptors alter muscle membrane potentials by stimulating bidirectional ion fluxes. In turn, membrane characteristics dictate whether the muscle cell contracts. (Adapted from Camilleri M, Phillips SF: Disorders of small intestinal motility. Gastroenterol Clin North Am 18:405, 1989, by permission of Mayo Foundation.)

Enteric and Extrinsic Nervous Supply to the Digestive Tract

In the mammalian digestive tract, the intrinsic (or enteric) nervous system (ENS) contains about 100 million neurons, approximately the number present in the spinal cord. This integrative system is organized in ganglionated plexuses (Fig. 14-2), which include the interstitial cells of Cajal (positive for ckit or tyrosine kinase) and fibroblast-like cells (positive for platelet-derived growth factor receptor α [PDGFRα]). Together, these cells constitute the *electrical syncytium* or the gastrointestinal pacemakers, integrating neuromuscular activity controlled by the ENS. The ENS is distinct and separate from the autonomic nervous system. It has several components: sensory mechanoreceptors and chemoreceptors, interneurons that process sensory input and control effector (motor and sensory) units, and effector secretor or motor neurons involved in secretory or motor functions of the gut.

Neural tissue in the gastrointestinal tract consists of nerve cell bodies and plexuses found in classically recognized plexuses, including the myenteric (Auerbach) plexus between the two muscular layers of the muscularis externa, and the submucosal (Meissner) plexus.

The myenteric plexus contains a large number of closely spaced ganglia interlinked by nerve-fiber bundles and extending from the pharyngoesophageal junction to the internal anal sphincter. Each ganglion contains a variable number of nerve cell bodies (up to 100). The submucosal plexus is confined to the small and large intestines and is composed of either large or small ganglia that are interlinked by internodal strands containing hundreds of axons.

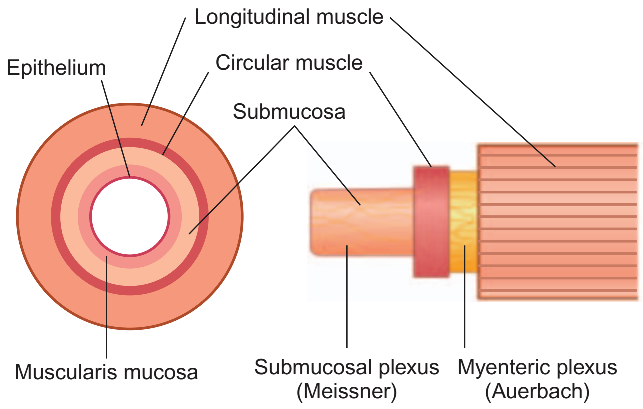

FIGURE 14-2 ■ The enteric plexuses in the intestinal layers. The chief neural plexuses are in the submucosal and intermuscular layers.

Preprogrammed neural circuits integrate motor function within and between different regions to coordinate gut functions. These functions include the peristaltic reflex and the interdigestive migrating motor complex (Fig. 14-1). The synaptic pathways in the gut wall respond to sensory input (e.g., by intraluminal content), and they can also be modulated by vagal and sacral (S2–4) preganglionic fibers (generally excitatory), and by sympathetic (T5–L2) postganglionic nerves (generally inhibitory to muscle layers, and excitatory to sphincters). There are approximately 40,000 preganglionic vagal fibers (many of which are afferent) at the level of the diaphragm. Loss of the sympathetic inhibitory control ("the brake") may manifest with gut motor overactivity, including diarrhea. Table 14-1 summarizes the wiring and functions of the extrinsic neural pathways to the digestive tract.

The Layers of the Gut

There are four layers (mucosa, submucosa, muscularis, and serosa) in the gut, with neural components between several layers. The mucosa is responsible for digestion and absorption and consists of the surface epithelium and the lamina propria. It is separated from the submucosa by the specialized, circumferential muscularis mucosae, which functions to allow surface absorptive cells to be in close contact with the intraluminal content. The submucosa consists of connective, lymphatic, and vascular tissue. The muscularis propria (or externa) is composed of an inner, thicker circular layer and an outer, thinner longitudinal layer. The longitudinal layer covers the entire circumference in the esophagus, small intestine, and rectum; in the colon, it is separated into three taeniae coli. In addition to these two layers, the stomach has a third oblique smooth muscle layer. The spindle-shaped smooth muscle cells are 40–100 μm long and 2–8 μm in diameter and are tightly packed with little connective tissue and with special contacts to allow for electrical coupling with the *electrical syncytium.* The gap junctions between the smooth muscle cells are essential, allowing sheets of muscle to be controlled by a few cells at the nerve–muscle interface. The serosa, which is the outermost layer, is composed of a thin sheet of mesothelial cells and connective tissue.

The literature on this topic is extensive. Older reference citations for specific statements made in this chapter can be found in prior editions.[1]

COMMON GASTROINTESTINAL SYMPTOMS IN NEUROLOGIC DISORDERS

Dysphagia

Dysphagia is the sensation of difficulty in swallowing. Oropharyngeal, or transfer, dysphagia is the inability to initiate a swallow or propel food from the mouth to the esophagus. The hold-up occurs high in the pharynx or esophagus and generally results from neurologic lesions affecting the swallow pathway rather than from a process affecting the oropharyngeal mucosa. Stroke and Parkinson disease are common causes; less commonly, other brainstem diseases (e.g., bulbar polio, Arnold–Chiari malformations, tumors) or muscle diseases (e.g., dystrophies and mitochondrial cytopathies) are responsible. Esophageal dysphagia is caused by abnormal esophageal peristalsis unrelated to the extrinsic neural supply, or to smooth muscle disorders (e.g., polymyositis).

Neuromuscular dysphagia typically results in dysphagia to both liquids and solids, and aspiration into the upper airways.

Physical examination shows evidence of the coexisting neurologic disease, such as abnormal palatal or pharyngeal movements or a brisk jaw jerk, suggesting pseudobulbar palsy. Barium videofluoroscopy or a fiberoptic endoscopic evaluation of swallowing can identify the motor and sensory disturbances, and may

TABLE 14-1 ■ Wiring and Functions of Extrinsic Neural Control

	Parasympathetic		Sympathetic		
Region	**Wiring**	**Function**	**Wiring**	**Function**	**Central Mechanism**
Esophagus					
Cervical	Vagus nerve; Recurrent laryngeal branch	Peristalsis in response to burst of spike activity	Superior cervical ganglion	Stimulation of UES tone	*Motor:* nucleus ambiguus, corticobulbar pathways
	Glossopharyngeal and vagus nerve	Sensation			*Sensory:* nucleus of tractus solitarius
Thoracic	Vagus nerve	Peristalsis by successive firing of vagal fibers	Celiac ganglion T6–9 spinal cord	Stimulation of LES tone	*Motor:* dorsal motor nucleus of vagus, corticobulbar pathways *Swallowing*: afferent modulation of central program
	Vagus nerve to nodose ganglia	Sensation			
Stomach	Vagus nerve	Peristalsis (cholinergic), inhibitory (nonadrenergic, e.g., receptive relaxation)	Celiac ganglion T6–9 spinal cord	Inhibition and relaxation (e.g., antrofundal reflex)	*Motor and sensory:* Dorsal motor nucleus of vagus, thoracic spinal cord; nucleus ambiguus
	Vagus nerve	Stretch and chemosensation	Spinal root ganglia T7–11	Mechanosensation (e.g., gastrogastric or enterogastric distention or nutrient reflexes)	
Small and large intestines	Vagus nerve	Small bowel and proximal colon peristalsis and sensation	Celiac ganglion to duodenum; superior and inferior mesenteric ganglia via splanchnic nerves to small bowel and via lumbar colonic nerves to colon; T9–10 spinal cord	Motor inhibition; distention reflexes	Nucleus of tractus solitarius (*sensory*), dorsal motor nucleus of vagus (*sensory and motor*); thoracic spinal cord; spinal cord base of dorsal horn (*motor parasympathetic*); parasympathetic nucleus (*sensory*)
	Sacral S2–4	Distal colon peristalsis and sensation			
Ileocecal sphincter	Vagus nerve	Sphincter contraction	Splanchnic and lumbar colonic nerves	Sphincter contraction (α effect); possibly also inhibitory β effect	T9–10 spinal cord; vagal nucleus (*motor*)
Anal sphincter					
Internal	S2–4	Sphincter relaxation	Lumbar splanchnic nerves; inferior mesenteric ganglia via hypogastric nerves	Sphincter contraction (α effect); possibly inhibitory β effect; ? participates in rectoanal inhibitory reflex; mediation of vesico-anal reflex	T9–10 spinal cord; spinal cord base of dorsal horn (*parasympathetic*)
External	S2–4 via pudendal nerves	Voluntary control; sensation			Lateral part of ventral horn of spinal cord (*motor and sensory*)

T, thoracic; S, sacral; UES, upper esophageal sphincter; LES, lower esophageal sphincter.
From Camilleri M: Autonomic regulation of gastrointestinal motility. p.105. In Low PA (ed) Clinical Autonomic Disorders: Evaluation and Management. 2nd Ed. Lippincott-Raven, Philadelphia, 1997, used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.

help stratify the risk of aspiration in patients with pharyngeal weakness. Pharyngoesophageal motility studies using solid-state pressure transducers also complement the diagnosis. Re-education of the swallowing process is feasible in many patients, often in a program that incorporates speech therapy. Nutritional support and prevention of bronchial aspiration are essential for those with more severe dysphagia not responding to conservative measures. This may require a gastrostomy feeding tube, which facilitates discharge from hospital, physical therapy, and rehabilitation. Since swallowing may improve considerably in the first 2 weeks after a stroke, long-term decisions should be delayed for that period.

Gastroparesis

Gastric motor dysfunction resulting in delayed gastric emptying is a common gastrointestinal manifestation of autonomic neuropathies, such as those associated with diabetes mellitus,[2,3] surgical vagotomy (e.g., laparoscopic fundoplication), and numerous medications, most commonly narcotic analgesics, tricyclic antidepressants, and dopamine agonists. Typical symptoms are recurrent postprandial nausea, emesis, and bloating, and pain resulting in weight loss and malnutrition. In diabetes mellitus, delayed gastric emptying may often be asymptomatic. Other stomach dysfunctions such as impaired gastric accommodation or gastric hypersensitivity may contribute to symptoms of gastroparesis (e.g., in diabetic patients). There may be a succussion splash on physical examination. It is essential to exclude gastric outlet obstruction by imaging the stomach or by endoscopy. Scintigraphic or stable isotope gastric emptying tests confirm delayed gastric emptying.[3] Gastric stasis in neurologic diseases may result from abnormal motility of the stomach or small bowel; studies of pressure profiles by manometry or solid-state pressure transducers (Fig. 14-3*A*) are rarely required to differentiate neuropathic from myopathic processes (Fig. 14-3*B*). Gastroparesis management includes the use of prokinetic agents, antiemetics, nutritional support, and interventions such as laparoscopic or endoscopic pyloroplasty.[3]

Chronic Intestinal Pseudo-Obstruction

Chronic intestinal pseudo-obstruction is a syndrome characterized by nausea, vomiting, early satiety, abdominal discomfort, weight loss, and altered bowel movements suggestive of intestinal obstruction in the absence of a mechanical obstruction. These symptoms are the consequence of abnormal intestinal motility, including from neurologic diseases extrinsic to the gut (e.g., disorders at any level of the neural axis), dysfunction of neurons in the myenteric plexus, or degeneration or malfunction of gut smooth muscle (Table 14-2). Use of narcotics, phenothiazines, dopaminergic agents, antihypertensive agents such as clonidine, and tricyclic antidepressants having anticholinergic effects may cause intestinal or colonic dysmotility.

The clinical features may suggest an underlying disease process. For example, postural dizziness, difficulties in visual accommodation in bright lights, sweating abnormalities, recurrent urinary infections, and problems with bladder voiding suggest an autonomic neuropathy. However, urinary manifestations are more commonly the result of the pelvic floor dysfunction that accompanies constipation, independent of any neurologic disease. Examination should evaluate pupillary reflexes to light and accommodation and the blood pressure and pulse in lying and standing positions; referral for autonomic reflex evaluation is important.

The combination of external ophthalmoplegia, high dysphagia, peripheral neuromyopathy (e.g., increased serum creatine kinase) and acidosis (e.g., increased lactate, pyruvate) suggests mitochondrial cytopathy, a rare disorder associated with small bowel pseudo-obstruction and diverticulosis.[4]

Plain radiographs and barium follow-through or computed tomographic (CT) or magnetic resonance (MR) enterography usually show nonspecific findings; dilatation of the small intestine is more frequent in later stages of myopathic than neuropathic disorders. The presence of small intestinal diverticula in a patient under 40 years should raise suspicion for mitochondrial cytopathy. Motility studies (Fig. 14-3) help differentiate myopathic and neuropathic processes. When a neuropathic process is identified, autonomic, radiologic, and serologic tests should be performed to identify the cause of the autonomic neuropathy or cerebrospinal disease (see later).

The goals of treatment of chronic intestinal pseudo-obstruction include the restoration of hydration and nutrition, stimulation of normal intestinal propulsion, and suppression of bacterial overgrowth when present (typically in myopathic disorders or in the presence of small bowel diverticula).

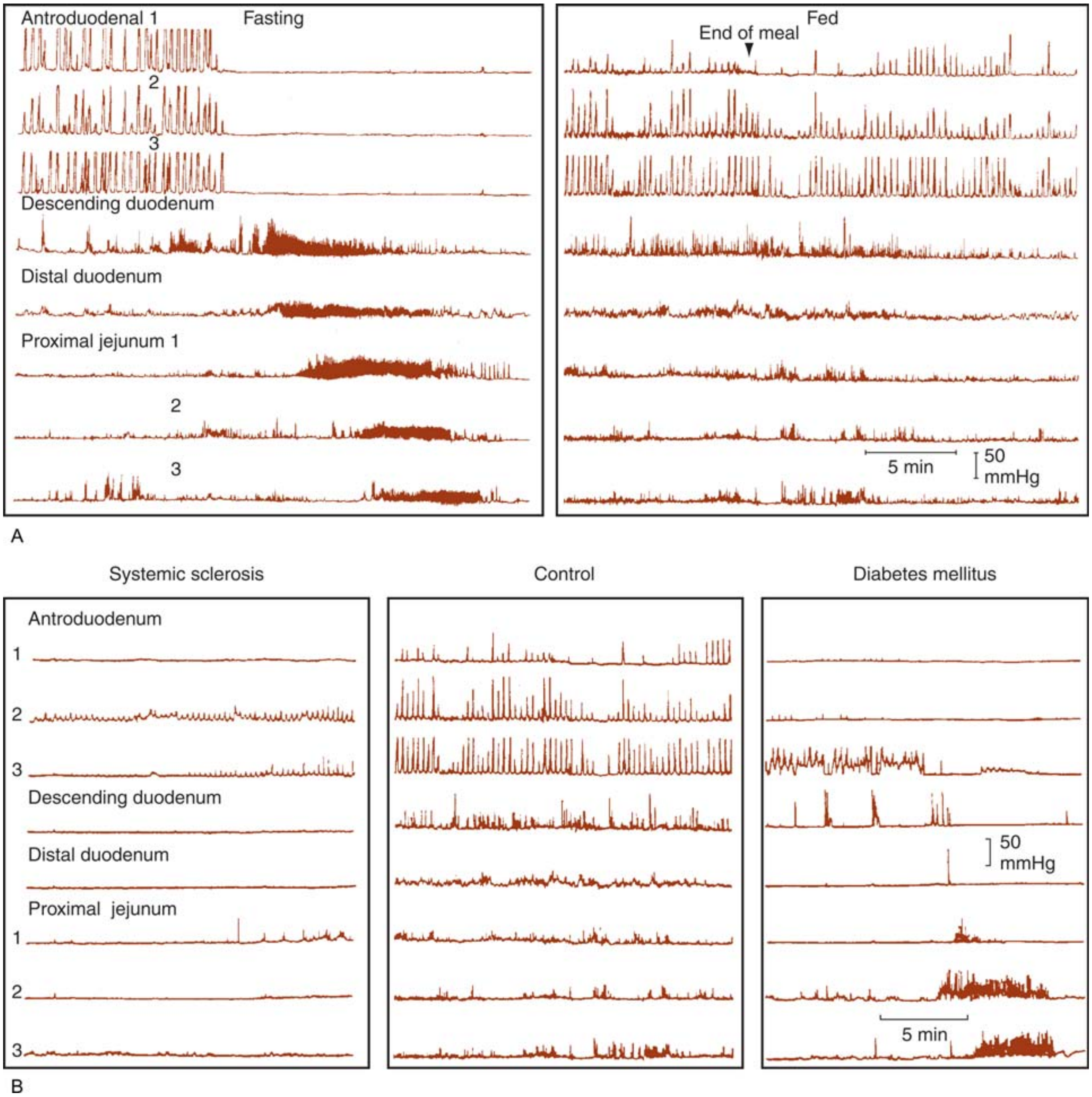

FIGURE 14-3 ■ *A*, Tracing showing normal upper gastrointestinal motility in the fasting and fed states. The fasting tracing shows phase III of the interdigestive migrating motor complex. *B*, Manometric tracings showing the myopathic pattern of intestinal pseudo-obstruction due to systemic sclerosis (*left panel*). Note the low amplitude of phasic pressure activity compared with control (*middle panel*). A manometric example of neuropathic intestinal pseudo-obstruction in diabetes mellitus shows the absence of antral contractions and persistence of cyclical fasting-type motility in the postprandial period (*right panel*). (*A*, From Malagelada J-R, Camilleri M, Stanghellini V: Manometric Diagnosis of Gastrointestinal Motility Disorders. Thieme, New York, 1986, by permission of Mayo Foundation. *B*, From Camilleri M: Medical treatment of chronic intestinal pseudo-obstruction. Pract Gastroenterol 15:10, 1991, with permission.)

Constipation

Constipation is a common complaint and may be perceived by the patient as infrequent bowel movements, excessively hard stools, the need to strain excessively during defecation, or a sense of incomplete evacuation after defecation. The need for enemas or finger evacuation to expel the stool from the lower rectum suggests a disturbance of the pelvic floor or anorectum. The co-existence of

TABLE 14-2 ■ Causes of Chronic Intestinal Pseudo-Obstruction

Cause	Myopathic	Neuropathic
Infiltrative	Progressive systemic sclerosis (PSS) Amyloidosis	Early PSS Amyloidosis
Familial	Familial visceral myopathies, including metabolic myopathies	Familial visceral neuropathies
General neurologic diseases	Myotonic and other dystrophies Mitochondrial cytopathies	Diabetes mellitus Porphyria Heavy metal poisoning Brainstem tumor Parkinson disease Multiple sclerosis Spinal cord transection
Infectious		Chagas disease Cytomegalovirus infection
Drug-induced		Tricyclic antidepressants Narcotic bowel syndrome
Neoplastic		Paraneoplastic (bronchial small cell carcinoma or carcinoid)
Idiopathic	Hollow visceral myopathy	Chronic intestinal pseudo-obstruction (possibly myenteric plexopathy)

incontinence and lack of rectal sensation suggests a neuropathy and is common among patients with diabetic neuropathy or disease affecting the lower thoracic cord (e.g., multiple sclerosis). The presence of blood in the stool with constipation necessitates further tests to exclude colonic mucosal lesions such as polyps, or perianal conditions such as hemorrhoids.

Broadly, constipation in neurologic disorders may be caused by potentially reversible factors (e.g., inadequate dietary fiber intake, lack of exercise, medications), slow colonic transit or pelvic floor dysfunction (i.e., a defecatory disorder) that may be related to the neurologic disorder, or another disease (e.g., colon cancer), or it may be a manifestation of functional disorder in patients who have a neurologic disease (Fig. 14-4). Many neurologic diseases (e.g., Parkinson disease, multiple sclerosis, spinal cord injury, and autonomic neuropathies) can affect colonic transit and pelvic floor functions or lead to diminished rectal sensation (e.g., due to a neuropathy or spinal cord injury).

The diagnosis and management of constipation in patients with neuromuscular disease include assessment of colonic anatomy, transit, and rectal evacuation.[5,6] Slow colonic transit occurs frequently in wheelchair- or bed-bound patients and may require, in addition, stimulant cathartics or prokinetic medications and scheduled rectal stimulation or enemas daily. In patients with paraplegia, computer-assisted sacral anterior root stimulation has been used to evoke sigmoid and rectal contraction coordinated with sphincter relaxation, which resembles normal defecation. This procedure reduces the time for defecation and the interval between defecations. A dorsal rhizotomy must be performed in such patients in order to avoid general stimulation of autonomic responses (autonomic dysreflexia), characterized by uncontrolled hypertension and bradycardia or tachycardia. This treatment is available at specialized centers. An alternative treatment for colonic inertia (severe neuromuscular dysfunction with absent response to food ingestion or intravenous neostigmine) may be subtotal colectomy with ileorectal anastomosis; however, if sphincter function is deficient and cannot be rehabilitated with physical therapy, a colostomy or ileostomy may be necessary. Other surgical procedures may correct a rectal prolapse or a rectocele.

Diarrhea

Diarrhea is defined as passage of abnormally liquid or unformed stools at an increased frequency, and is termed “chronic” if more than 4 weeks in duration. Acute diarrhea in neurologic patients is most frequently caused by infectious agents or medications. The differential diagnosis of chronic diarrhea is discussed in detail elsewhere.[7] In autonomic neuropathies, as in patients with diabetic neuropathy, chronic diarrhea is often multifactorial and may be associated with intake of osmotic agents (e.g., artificial sweeteners), secretion, malabsorption secondary to rapid transit (possibly due to sympathetic denervation), small bowel bacterial overgrowth, bile acid diarrhea, and high-amplitude propulsive contractions in the colon that result in urgency and sometimes incontinence of stool.

Generally, the aid of a gastroenterologist is necessary to evaluate patients and guide diagnostic tests. Features of fat malabsorption (e.g., greasy, difficult-to-flush stools, weight loss) should prompt measurement of 48-hour stool fat and total stool bile acids. The

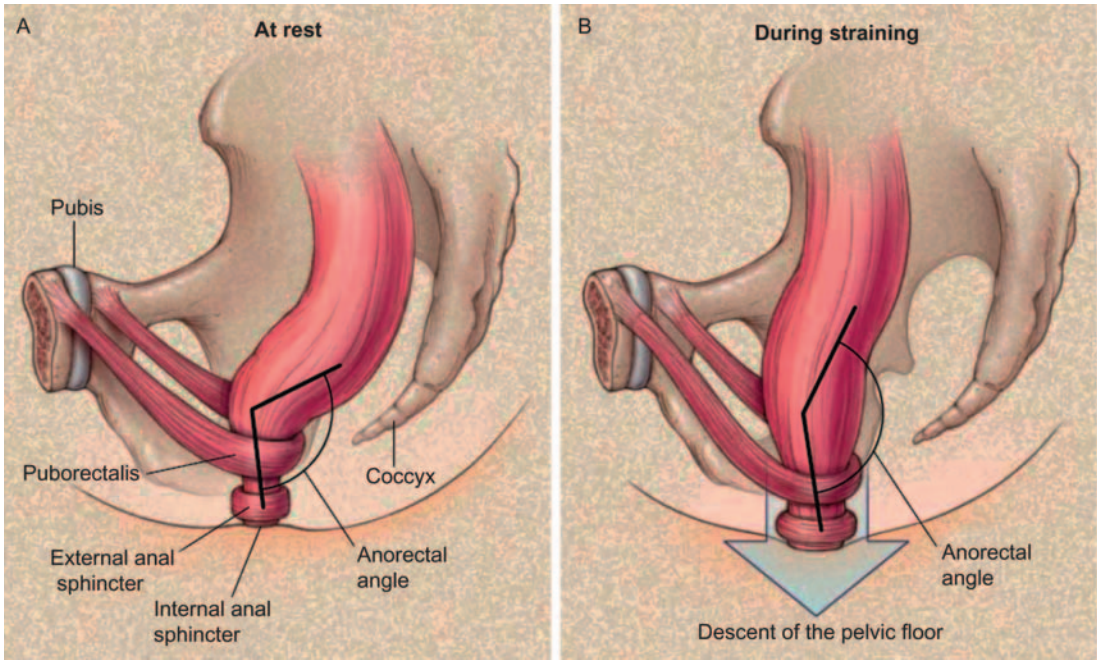

FIGURE 14-4 ■ Schema showing pelvic floor, rectoanal angle, and sphincters at rest (*A*) and normal alterations during defecation (*B*). (From Lembo T, Camilleri M: Chronic constipation. N Engl J Med 349:1360, 2003, with permission.)

co-existence of diarrhea and neurologic manifestations may be explained by autonomic dysfunction (e.g., in diabetic neuropathy), the neurologic consequences of malabsorption (e.g., myopathy or neuropathy in celiac disease or bacterial overgrowth), and rare diseases with neurologic manifestations (e.g., Whipple disease). After excluding a structural cause (e.g., inflammatory bowel disease) and malabsorption, most patients with diarrhea due to disordered motility can be treated effectively with the peripheral μ-opioid receptor agonist, loperamide, beginning with 2 mg taken 30 minutes before meals, and titrated to control symptoms up to a maximum of 16 mg daily. The α_2-adrenergic agonist, clonidine, reduces diarrhea by improving intestinal absorption, inhibiting intestinal and colonic motility, and enhancing resting anal sphincter tone; however, it aggravates postural hypotension, even when administered by transdermal patch. Other agents to be considered are oral bile acid sequestrants (e.g., cholestyramine and colesevelam) and subcutaneous octreotide.

Fecal Incontinence

Fecal incontinence may result from multiple sclerosis, Parkinson disease, multiple system atrophy, Alzheimer disease, stroke, diabetic neuropathy, and spinal cord lesions. In addition to generalized neuropathies (e.g., diabetes), obstetric trauma and stretch-induced pudendal nerve injury related to excessive straining in constipated patients are other causes of a pudendal neuropathy.[8–11] Incontinence occurring only at night suggests internal anal sphincter dysfunction (e.g., progressive systemic sclerosis, diabetic neuropathy); stress incontinence during coughing, sneezing, or laughing suggests loss of external sphincter control, typically from pudendal nerve or S2, S3, and S4 root lesions. Leakage of formed stool suggests more severe sphincter weakness than leakage of liquid stool alone.

Examination of the incontinent patient should include inspection of the anus with and without straining to detect rectal prolapse, a digital rectal examination, and proctoscopy to exclude impaction or mucosal disease. Anal examination may disclose normal (e.g., multiple sclerosis) or reduced (e.g., diabetes mellitus, scleroderma) anal resting tone. The external sphincter and puborectalis contractile responses during squeeze are reduced, and the perianal wink reflex is absent in conditions affecting the lower spinal cord or pudendal nerves. Perineal weakness is often manifested by excessive perineal descent (> 4 cm) on straining.

In evaluating such patients, it is important first to exclude overflow incontinence due to fecal impaction;

overuse of laxatives or magnesium-containing antacids may also be responsible. If these are not identified, further tests may be necessary: anorectal manometry, rectal sensation, ability to expel a balloon from the rectum, endoanal ultrasound or MRI to identify anal sphincter defects, and dynamic barium or MR defecography to identify rectal evacuation and anatomic abnormalities (e.g., rectocele, rectal intussusception). EMG of the anal sphincter is rarely required, usually to prove evidence of denervation (fibrillation potentials), myopathic damage (small polyphasic motor unit potentials), neurogenic damage (large polyphasic motor unit potentials), or mixed injury.[12,13]

Medical management includes perianal hygiene, protective devices to maintain skin integrity, and restoration of regular bowel habits. Biofeedback therapy has little impact in patients with weak anal sphincters or poor rectal sensation. Clonidine may help some patients by increasing consistency of stool and increasing resting anal sphincter tone, if it is tolerated. A colostomy may be necessary in patients with medically refractory fecal incontinence. Before resorting to this, it is important to exclude mucosal prolapse in association with incontinence, since surgical correction of the prolapse may temporarily improve continence by permitting better function of the external sphincter.[14] More complex surgical procedures (i.e., artificial anal sphincter, dynamic graciloplasty) are not routinely performed. Injection of bulking agents such as silicone biomaterial (PTQ) or carbon-coated beads (Durasphere) for fecal incontinence is used following obstetric anal sphincter injury, but has not been extensively tested in primary neurologic disease. Sacral nerve stimulation can improve symptoms, anal pressures, and rectal sensation, even in patients with neurogenic fecal incontinence. In the future, it is hoped that stem cells combined with normal cells on bioengineered scaffolds may result in successful creation and implantation of intrinsically innervated anal sphincter constructs.

EXTRINSIC NEUROLOGIC DISORDERS CAUSING GUT DYSMOTILITY

Certain diseases affect both intrinsic and extrinsic neural control. This review concentrates on diseases of extrinsic neural control and smooth muscle. Diseases affecting the enteric nervous system are reviewed elsewhere.

Brain Diseases

STROKE

Dysphagia may result from cranial nerve involvement and may cause malnutrition or aspiration pneumonia. Videofluoroscopy of the pharynx and upper esophagus typically shows transfer dysphagia or tracheal aspiration. Colonic pseudo-obstruction occurs rarely. Percutaneous endoscopic gastrostomy is usually the most effective method to provide nutrition without interfering with rehabilitation; feedings can be given in the forms of boluses or by infusion at night. Swallowing improves in a majority of survivors over 1 week to 3 months. The severity of the initial neurologic deficit is the strongest predictor of eventual recovery. The gastrostomy tube can be removed when oral intake is shown to be sufficient to maintain caloric requirements.

ALZHEIMER DISEASE

In a retrospective population-based study, people with Alzheimer disease, aged 65 years and older, had a higher incidence of serious upper and lower gastrointestinal (GI) events including ulceration, perforation, and bleeding than a well-matched random sample of people without Alzheimer disease. The association was also present in participants without a history of GI bleeding. Treatment of Alzheimer disease with the acetylcholinesterase medications, such as donepezil or rivastigmine, is associated with gastrointestinal symptoms, such as nausea, vomiting, and diarrhea. These may be dose related and may be reduced by using transdermal preparations.

PARKINSONISM

Patients with Parkinson disease experience several gastrointestinal manifestations. These include salivary drooling (sialorrhea) which is often associated with speech and eating impairment; dysphagia; gastroparesis; constipation; and anorectal dysfunction including incontinence. The prevalence of gastrointestinal symptoms is related to disease duration and severity, rather than to diet or treatment. Constipation may precede by several years the development of motor symptoms.

Excessive salivary drooling may respond to systemic or topical anticholinergic agents that reduce production of saliva.

Abnormal swallowing results mainly from impaired pharyngeal and upper esophageal muscle function.

It is associated frequently with choking, disordered salivation, and variable degrees of malnutrition. Moderate dysphagia may be diagnosed by videofluoroscopy (oropharyngeal and esophageal) or esophageal manometry. Conservative treatment includes attention to the consistency of food (thickened liquids) and to adequate caloric content of meals. With more severe dysphagia, expiratory muscle strength training and video-assisted swallowing therapy may be effective alone or with dopaminergic therapy, and a percutaneous gastrostomy may be necessary.

Delayed gastric emptying can influence levodopa pharmacokinetics and may itself be aggravated by levodopa. Domperidone, a D2 receptor antagonist, does not cross the blood–brain barrier and may help gastroparesis, but it is not widely available and increases the risk of cardiac arrhythmia. To reduce levodopa pharmacokinetic derangements, options include liquid formulations of the medication, intestinal gels, and dopamine agonist skin patches. The bioavailability of other medications can be altered considerably by the effects of parkinsonism on gut transit and delivery of medications to the small bowel for absorption.

Several factors lead to constipation in Parkinson disease: generalized hypokinesia, gut hypomotility, anal sphincter or defecatory dysfunction, and effects of anticholinergic and dopamine agonists. Constipation manifests as decreased stool frequency, disturbed stool consistency, and excessive straining. Constipation may precede the development of somatic motor symptoms by several years. Patients with Parkinson disease or progressive supranuclear palsy may also have oropharyngeal dysfunction with impaired swallowing.

The gut is a portal of entry for prions leading to neurologic diseases such as Alzheimer and Parkinson disease and transmissible spongiform encephalopathies. Neuropathologic studies have shown early accumulation of abnormal inclusions containing α-synuclein (Lewy neurites) in the enteric nervous system and dorsal motor nucleus of the vagus, in both Parkinson and incidental Lewy body disease. Colonic biopsies may show accumulation of α-synuclein immunoreactive Lewy neurites in the submucosal plexus of patients with Parkinson disease. However, α-synuclein is abundantly expressed in all nerve plexuses of the human ENS, especially with increasing age and therefore may not be regarded as a pathologic correlate.

HEAD INJURY

Immediately following moderate to severe head injury, most patients develop transient delays in gastric emptying. The underlying mechanism is unknown, although a correlation exists between the severity of injury, increased intracranial pressure, and severity of the gastric stasis. These patients are frequently intolerant of enteral feeding and may require parenteral nutrition temporarily. Enteral nutrition can often be reintroduced within a few weeks.

AUTONOMIC EPILEPSY AND MIGRAINE

Autonomic epilepsy and migraine are infrequent causes of upper abdominal symptoms, such as nausea and vomiting. Treatment is of the underlying neurologic disorder.

AMYOTROPHIC LATERAL SCLEROSIS

Patients with amyotrophic lateral sclerosis and progressive bulbar palsy have predominant weakness of the muscles supplied by the glossopharyngeal and vagus nerves. Dysphagia is a frequent complaint, and patients may have respiratory difficulty while eating as a result of aspiration or respiratory muscle fatigue. Rarely, patients with vagal dysfunction develop chronic intestinal pseudo-obstruction.

Physical examination reveals cranial nerve palsies, muscle fasciculations, or an exaggerated jaw jerk. Videofluoroscopic barium swallow of liquids and solids is employed to evaluate swallowing, determine whether aspiration occurs, and guide decisions about the route to use for nutritional support (oral feeding or a percutaneous gastrostomy). Cervical esophagostomy or cricopharyngeal myotomy have been performed in selected cases for significant cricopharyngeal muscle dysfunction.

POSTPOLIO DYSPHAGIA

Patients with postpolio syndrome frequently have dysphagia and aspiration, especially if there was bulbar involvement during the initial attack. Videofluoroscopy is useful for screening and monitoring progression of disease. Attention to the position of the patient's head during swallowing and alteration of food consistency to a semisolid state can decrease the prevalence of choking and aspiration.

BRAINSTEM LESIONS

Brainstem lesions can present with isolated gastrointestinal motor dysfunction. Compression of the brainstem and lower cranial nerves can cause potentially life-threatening neurogenic dysphagia in patients with Arnold–Chiari malformations. In the absence of increased intracranial pressure, gastrointestinal symptoms in association with brain tumors typically result from distortion of the vomiting center on the floor of the fourth ventricle, which leads to delay in gastric emptying. Although vomiting is the most common symptom, colonic and anorectal dysfunctions have also been described. The presence of more widespread autonomic dysfunction, particularly if preganglionic sympathetic nerves are involved (as shown on a thermoregulatory sweat test), necessitates a search for a structural lesion in the central nervous system.

Autonomic System Degenerations

PANDYSAUTONOMIAS OR SELECTIVE DYSAUTONOMIAS

Pandysautonomias are characterized by preganglionic or postganglionic lesions affecting both the sympathetic and parasympathetic nervous systems. Vomiting, paralytic ileus, constipation, and a chronic pseudo-obstruction syndrome have been reported in acute, subacute, and congenital pandysautonomia. Selective cholinergic dysautonomia may also impair upper and lower gastrointestinal motor activity. This picture usually follows a viral infection such as infectious mononucleosis or influenza A.

IDIOPATHIC ORTHOSTATIC HYPOTENSION

Idiopathic orthostatic hypotension is sometimes associated with motor dysfunction of the gut, such as esophageal dysmotility, gastric stasis, alteration in bowel movements, and fecal incontinence. Cardiovascular and sudomotor abnormalities usually precede gut involvement. The precise site of the lesion causing the gut dysmotility is unknown.

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

About one-third of patients with postural orthostatic tachycardia syndrome have gastrointestinal manifestations, including pseudo-obstruction syndrome. It is important to exclude dehydration, deconditioning, and functional gastrointestinal disorders that produce similar clinical features.

MULTIPLE SYSTEM ATROPHY

In the original description of this disorder, constipation and fecal incontinence were included among its classic features. Abnormal esophageal motility was demonstrated by videofluoroscopy and by the occurrence of frequent, simultaneous, low-amplitude peristaltic waves on esophageal manometry. Fasting and postprandial antral and small bowel motility may be reduced.

Spinal Cord Lesions

SPINAL CORD INJURY

Dysphagia after acute cervical spinal cord injury (SCI) generally improves during the initial hospitalization.

Ileus is a frequent finding soon after spinal cord injury, but it is rarely prolonged. Acalculous cholecystitis occurs in 3.7 percent of patients with acute SCI.

Bowel problems occur in 27 to 62 percent of patients with SCI, most commonly constipation, distention, abdominal pain, rectal bleeding, hemorrhoids, fecal incontinence, and autonomic hyperreflexia; gallstones occur in 17 to 31 percent of patients. In the chronic phase after injury, disorders of upper gastrointestinal motility are uncommon, whereas colonic and anorectal dysfunctions are common. The latter probably result from interruption of supraspinal control of the sacral parasympathetic supply to the colon, pelvic floor, and anal sphincters. After thoracic SCI, colonic compliance and postprandial colonic motor responses may be reduced. The loss of voluntary control of defecation may be the most significant disturbance in patients who rely on reflex rectal stimulation for stool evacuation. Fecal impaction may present with anorexia and nausea. Diverticula, internal hemorrhoids, and polyps in veterans with SCI were associated with time elapsed since SCI; however, in a small study, these complications were not more prevalent than in non-SCI veterans matched for age, sex, and race/ethnicity.

Loss of control of the external anal sphincter commonly results in fecal incontinence after SCI.

The usual management for irregular bowel function is a combination of laxatives, bulking agents, anal massage, manual evacuation, and scheduled enemas, which may contain chemical stimulants such as bisacodyl (10 mg in a 30 ml enema). Randomized, double-blind studies demonstrated the effectiveness of neostigmine, which increases cholinergic tone, combined with glycopyrrolate, an anticholinergic agent with minimal activity in the colon that reduces extracolonic side effects. Computerized stimulation of the sacral anterior roots may restore normal function to the pelvic colon and anorectal sphincters; this anterior sacral root stimulation may be combined with S2 to S4 posterior sacral rhizotomy in order to interrupt the spasticity-causing sensory nerves and avoid autonomic dysreflexia. If these measures are unavailable or ineffective and severe constipation persists, a colostomy reduces time for bowel care and avoidance or healing of decubitus ulcers.

The acute abdomen may be a significant challenge in SCI, with mortality of 9.5 percent in one series. In SCI patients, acute abdominal conditions do not present with rigidity or absent bowel sounds, but with dull or poorly localized pain, vomiting, or restlessness, with tenderness, fever, and leukocytosis in up to 50 percent of patients.

MULTIPLE SCLEROSIS

Severe constipation (typically slow transit) frequently accompanies urinary bladder dysfunction in patients with advanced multiple sclerosis; there may be fecal incontinence even in patients with constipation. Impaired function of the supraspinal or descending pathways that control the sacral parasympathetic outflow may impair colonic motor dysfunction or affect defecation. Motility disturbances are more frequent in the lower than in the upper gut.

Constipation and fecal incontinence may co-exist and alternate, impacting on the patient's quality of life and social interactions. Anorectal manometry is helpful to differentiate anal sphincter hypotonia, rectal hyposensitivity (both causes of incontinence), and pelvic floor dyssynergia as the cause of constipation, which may be complicated by "overflow" incontinence. Rectal compliance correlates with overall disability from multiple sclerosis, and observed alterations in rectal properties are secondary to spinal cord involvement. Transanal irrigation or lower bowel stimulation (with stimulant agents, as for SCI patients) may be required to relieve the constipation and clear the lower bowel to avoid incontinence episodes.

NEUROMYELITIS OPTICA

Area postrema (including morphologic evidence of aquaporin-4 [AQP4] autoimmunity) may be a selective target of the disease process in neuromyelitis optica. These findings are compatible with clinical reports of nausea and vomiting preceding episodes of optic neuritis and transverse myelitis or being the heralding symptom of the disorder.

Peripheral Neuropathy

ACUTE PERIPHERAL NEUROPATHY

Autonomic dysfunction associated with certain acute viral infections may result in nausea, vomiting, abdominal cramps, constipation, or a clinical picture of pseudo-obstruction. In the Guillain–Barré syndrome, visceral involvement may include gastric distention or adynamic ileus. Persistent gastrointestinal motor disturbances may also occur in association with herpes zoster, Epstein–Barr virus infection, or botulism B. The site of the neurologic lesion is uncertain. Cytomegalovirus has been identified in the myenteric plexus in some patients with chronic intestinal pseudo-obstruction. Selective cholinergic dysautonomia (with associated gastrointestinal dysfunction) has been reported to develop within a week of the onset of infectious mononucleosis. Diarrhea induced by human immunodeficiency virus (HIV) may be another manifestation of autonomic dysfunction (see later), but the data require confirmation.

CHRONIC PERIPHERAL NEUROPATHY

Chronic peripheral neuropathy is the most commonly encountered extrinsic neurologic disorder that results in gastrointestinal motor dysfunction.

Diabetes Mellitus

Diabetic autonomic neuropathy of the gut has been studied extensively and has been reviewed elsewhere. In patients with type I diabetes mellitus seen at university medical centers, gastrointestinal symptoms, particularly constipation, are quite common. A US-based study in the community showed that constipation, with or without the use of laxatives, was the only gut symptom more frequent in patients with type I diabetes mellitus than in age- and sex-matched controls. Patients with constipation tended to be taking medications that cause the symptoms or to have bladder symptoms.

Gastric emptying of digestible or nondigestible solids is abnormal in patients with diabetes mellitus and gastrointestinal symptoms ("gastroparesis"). There is a paucity of distal antral contractions during fasting and postprandially; small bowel motility may also be abnormal. These features are consistent with an "autovagotomy," or loss of the interstitial cells of Cajal (pacemaker cells) associated with an imbalance in the local macrophage cells that protect the neural elements from the effects of oxidative stress.

Constipation among community diabetics was associated equally with slow transit, normal transit, or pelvic floor dysfunction. Diarrhea or fecal incontinence (or both) may result from several mechanisms: dysfunction of the anorectal sphincter or abnormal rectal sensation, osmotic diarrhea from bacterial overgrowth due to small bowel stasis, rapid transit from uncoordinated small bowel motor activity, or the intake of artificial sweeteners such as sorbitol. Rarely, an associated gluten-sensitive enteropathy or pancreatic exocrine insufficiency is present.

Histopathologic studies of the vagus nerve have revealed a reduction in the number of unmyelinated axons; surviving axons are usually of small caliber. In patients with diabetic diarrhea, there are giant sympathetic neurons and dendritic swelling of the postganglionic neurons in prevertebral and paravertebral sympathetic ganglia as well as reduced fiber density in the splanchnic nerves.

Treatment of gastroparesis follows guidelines reviewed elsewhere, and therapeutic options have resulted in only transient relief. Pancreas transplantation is reported to restore normal gastric emptying in patients with diabetic gastroparesis. Long-term results are not available, however, and the gastric stasis and autonomic neuropathy may not be resolved with the pancreas transplant.

Paraneoplastic Neuropathy

Autonomic neuropathy and gastrointestinal symptoms may occur in association with small cell carcinoma of the lung or pulmonary carcinoid. In one series, all seven patients suffered constipation, six had gastroparesis, four had esophageal dysmotility suggestive of spasm or achalasia, and two had other evidence of autonomic neuropathy that affected bladder and blood pressure control. There are circulating IgG antibodies (e.g., ANNA-1 or anti-Hu) directed against enteric neuronal nuclei, suggesting that the enteric plexus is the major target of this paraneoplastic phenomenon. However, several patients have also had evidence of extrinsic visceral neuropathies, suggesting a more extensive neuropathologic process. The chest x-ray is frequently normal in these patients; a chest computed tomography (CT) scan is therefore indicated when the syndrome is suspected, typically in middle-aged smokers with recent onset of nausea, vomiting, or feeding intolerance. Whole-body fluorodeoxyglucose positron emission tomography (FDG-PET) or FDG-PET/computed tomography may be helpful for detecting malignancies that cannot be detected by conventional screening tests. In other reports, however, there has not been FDG uptake in the tumor or metastases.

Ganglionic receptor-binding antibodies have also been found in a subset of patients with idiopathic, paraneoplastic, or diabetic autonomic neuropathy and idiopathic gastrointestinal dysmotility; the antibody titer correlated with more severe autonomic dysfunction. This autoimmune model of gastrointestinal dysmotility has been replicated in an animal model.

Immunomodulatory treatment before, during, or after antineoplastic therapy may be of benefit for patients with paraneoplastic neuropathy and has been used even when the underlying malignancy cannot be identified.

Amyloid Neuropathy

Gastrointestinal disease in amyloidosis results from either mucosal infiltration or neuromuscular infiltration. In addition, an extrinsic autonomic neuropathy may also affect gut function. A retrospective series reported that 76 of 2,334 (3.2%) patients with amyloidosis had biopsy-proven amyloid involvement of the gastrointestinal tract. Of these 76 patients, 79 percent had systemic amyloidosis while 21 percent had GI amyloidosis without evidence of an associated plasma cell dyscrasia or other organ involvement. Amyloid neuropathy may lead to constipation, diarrhea, and steatorrhea. Patients have uncoordinated nonpropagated contractions in the small bowel.

These features are similar to the intestinal myoelectric disturbances observed in animals subjected to ganglionectomy. Familial amyloidosis may also affect the gut.

Manometric studies and monitoring of the acute effects of cholinomimetic agents can distinguish between neuropathic (uncoordinated but normal-amplitude pressure activity) and myopathic (low-amplitude pressure activity) types of amyloid gastroenteropathy. These strategies may identify patients (i.e., those with the neuropathic variant) who are more likely to respond to prokinetic agents. The effects of advanced therapies for amyloidosis (autologous or allogeneic stem cell transplantation in combination with cytotoxic therapy) on gastrointestinal dysmotility are unclear.

Chronic Sensory and Autonomic Neuropathy of Unknown Cause

This is a rare, nonfamilial form of slowly progressive neuropathy that affects a number of autonomic functions. Patients may exhibit only a chronic autonomic disturbance (e.g., abnormal sudomotor, vasomotor, or gastrointestinal function) for many years before peripheral sensory symptoms develop. Autonomic dysfunction is probably responsible for functional gastrointestinal motor disorders when these develop prior to the onset of more obvious features of dysautonomia. This may account for a subset of patients with symptoms suggestive of irritable bowel syndrome.

A high nicotinic acetylcholine receptor antibody titer with postganglionic autonomic damage and evidence of somatic nerve fiber involvement suggests that such cases may have an immune etiology, as is discussed later.

Some investigators have reported familial cases of intestinal pseudo-obstruction with degeneration of the myenteric plexus and evidence of sensory or motor neuropathies affecting peripheral or cranial nerves.

Porphyria

Acute intermittent porphyria and hereditary coproporphyria frequently present with abdominal pain, nausea, vomiting, and constipation. Porphyric polyneuropathy may lead to dilatation and impaired motor function in any part of the intestinal tract, presumably because of autonomic dysfunction. Effects of porphyria on the enteric nervous system have not been described.

Neurofibromatosis

Children with neurofibromatosis type 1 frequently have symptoms of constipation, which can be associated with enlarged rectal diameter and prolonged colonic transit time.

Human Immunodeficiency Virus Infection

Neurologic disease may manifest at any phase of HIV infection. Chronic diarrhea may result from increased extrinsic parasympathetic activity to the gut or damage to adrenergic fibers within the enteric plexuses. Further studies are needed to characterize these abnormalities; it is, of course, important to exclude gut infections and infestations in patients with HIV seropositivity and diarrhea.

Autoimmune Neuropathies

Autoimmune neuropathies are rare causes of gastrointestinal dysmotilities.

Antibodies to Ganglionic Acetylcholine Receptors

Antibodies that bind to or block ganglionic acetylcholine receptors have been identified in patients with various forms of autoimmune autonomic neuropathy. In one series, 9 percent of patients with idiopathic GI dysmotility had antibodies toward ganglionic acetylcholine receptors, and antibody titers were positively correlated with the severity of autonomic dysfunction, suggesting a pathogenic role. Moreover, passive transfer of ganglionic AChR-specific IgG impaired autonomic synaptic transmission and caused autonomic dysfunction in mice. The antibody effect was potentially reversible, suggesting that early use of immunomodulatory therapy directed at lowering IgG levels and abrogating IgG production may be therapeutically effective in patients with autoimmune autonomic neuropathy.

Antibodies to Specific Ion Channels

Autoantibodies directed against specific neural antigens, including ion channels, may be associated with gut motility disorders including esophageal dysmotility, slow transit constipation, and chronic intestinal pseudo-obstruction. Among 33 patients with ganglionitis shown on full-thickness jejunal laparoscopic biopsies, two patients with symptoms of irritable bowel syndrome had antibodies directed towards neuronal ion channels (one against voltage-gated potassium channels and the other against neuronal alpha3-AChR). The pathogenic role of such antibodies requires further determination. Similarly, in pediatric patients with suspected neurologic autoimmunity, there was a minority (<3%) with serum positive for neuronal potassium channel complex-reactive immunoglobulin G and, among these, two of seven patients had gastrointestinal dysmotility.[15]

Similar ion channel or acetylcholine receptor antibodies were reported in 24 patients with GI motility disorders (such as achalasia and delayed gastric emptying); 11 patients had associated malignancies.[16] The prevalence of these antibodies is not higher in community-based patients with irritable bowel syndrome or functional dyspepsia than in asymptomatic controls. Antibodies against voltage-gated potassium channels (particularly CASPR2-IgG-positivity) are also associated with chronic idiopathic pain and hyperexcitability of nociceptive pathways; however, there is no association with significant gastrointestinal pain.

GENERAL MUSCLE DISEASES CAUSING GUT DYSMOTILITY

At an advanced stage, progressive systemic sclerosis and amyloidosis result in an infiltrative replacement of smooth muscle cells in the digestive tract. Rarely, Duchenne or Becker muscular dystrophy and polymyositis or dermatomyositis have been associated with gastroparesis. There are a number of case or family reports of chronic intestinal pseudo-obstruction, sometimes in association with an external ophthalmoplegia, secondary to a mitochondrial myopathy. Patients with myotonic dystrophy may have megacolon; anal sphincter dysfunction also occurs and is consistent with an expression of myopathy, muscular atrophy, and neural abnormalities. The myopathic nature of these disorders is reflected by the low-amplitude contractions that occur at affected levels of the gut, as studied especially in systemic sclerosis.

Myopathic disorders may be complicated by bacterial overgrowth and small bowel diverticula; pneumatosis cystoides intestinalis and spontaneous pneumoperitoneum sometimes occur in progressive systemic sclerosis. However, it is worth noting that systemic sclerosis affects the gut from the distal two-thirds of the esophagus to the anorectum; thus, it may present with dysphagia (which may also be due to reflux esophagitis and stricture), gastric stasis, chronic intestinal pseudo-obstruction, steatorrhea due to bacterial overgrowth, constipation, incontinence (particularly at night, owing to involvement of the internal anal sphincter), and rectal prolapse. Skeletal muscle electromyography (EMG) or biopsy may be needed to establish the nature of the generalized neuromuscular disorder, as in mitochondrial myopathy. Treatment includes restoration of nutrition (which may necessitate total parenteral nutrition), suppression of bacterial overgrowth, and treatment of complications such as gastroesophageal reflux (with proton pump inhibitor) or esophageal strictures (by endoscopic dilatation). Colonic dilatation and intractable constipation may necessitate subtotal colectomy with ileorectostomy. Prokinetics are rarely effective but should at least be tried. The somatostatin analogue octreotide improves symptoms in the short term and may suppress bacterial overgrowth. However, octreotide retards postprandial small bowel transit. We use it only once per day, at least 3 hours after the last meal, to induce migrating motor activity and clear residue from the stomach and small bowel.

Allogeneic stem cell transplantation has been proposed as an early treatment for mitochondrial neurogastrointestinal encephalomyopathy while patients are still relatively healthy. In two patients, post-transplant clinical follow-up showed improvement in gastrointestinal dysmotility, abdominal cramps, and diarrhea.

IDENTIFICATION OF EXTRINSIC NEUROLOGIC DISEASE WITH GASTROINTESTINAL SYMPTOMS OF DYSMOTILITY

Patients with lesions at virtually any level of the nervous system may have symptoms of gastrointestinal motor dysfunction. Therefore, a strategy is necessary in the diagnostic evaluation of disordered gastrointestinal function (Fig. 14-5). Here there is convergence of the paths of the neurologist and gastroenterologist. Patients should undergo further testing, particularly if they have clinical features suggestive of autonomic or peripheral nerve dysfunction or a known underlying neuromuscular disorder. It is essential to record the use of all medications that influence gut motility.

Gastrointestinal motility and transit measurements help the clinician to objectively confirm the disturbance in the motor function of the gut and distinguish between neuropathic and myopathic disorders.

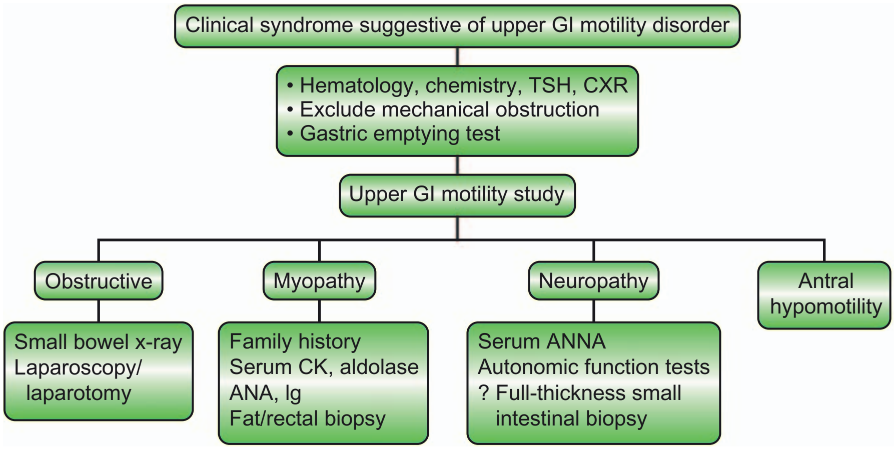
Clinical syndrome suggestive of upper GI motility disorder
• Hematology, chemistry, TSH, CXR
• Exclude mechanical obstruction
• Gastric emptying test
Upper GI motility study
Obstructive
Myopathy
Neuropathy
Antral hypomotility
Small bowel x-ray
Laparoscopy/ laparotomy
Family history
Serum CK, aldolase
ANA, Ig
Fat/rectal biopsy
Serum ANNA
Autonomic function tests
? Full-thickness small intestinal biopsy

FIGURE 14-5 ■ Algorithm for the investigation of suspected gastrointestinal (GI) dysmotility. ANA, antinuclear antibodies; ANNA, antineuronal enteric antibodies; CK, creatine kinase; CXR, chest radiograph; Ig, immunoglobulin; TSH, thyroid-stimulating hormone. (From Camilleri M: Study of human gastroduodenojejunal motility: applied physiology in clinical practice. Dig Dis Sci 38:785, 1993, with permission.)

Tests of autonomic function (see Chapter 8) are useful for identifying the extent of involvement and localizing the anatomic level of the disturbance in extrinsic neural control. There is generally good agreement between abnormalities of abdominal vagal function, including the plasma pancreatic polypeptide response to modified sham feeding (Fig. 14-6) and cardiovagal dysfunction in patients with diabetes. When defects of the sympathetic nervous system have been identified by conventional tests, these usually reflect postganglionic dysfunction as in peripheral or autonomic neuropathy. An abnormal sweat test with normal sudomotor axon reflex test suggests a disturbance of preganglionic nerves and should be further investigated, for example, by imaging brain and spinal cord.

Once visceral autonomic neuropathy is identified, further tests are needed to identify any occult causes of the neuropathy; examples include lung tumors (CT of the chest), porphyria (uroporphyrinogen-1-synthase and coproporphyrinogen oxidase in erythrocytes), and amyloidosis (special protein studies in blood and urine, fat, or a rectal biopsy specimen).

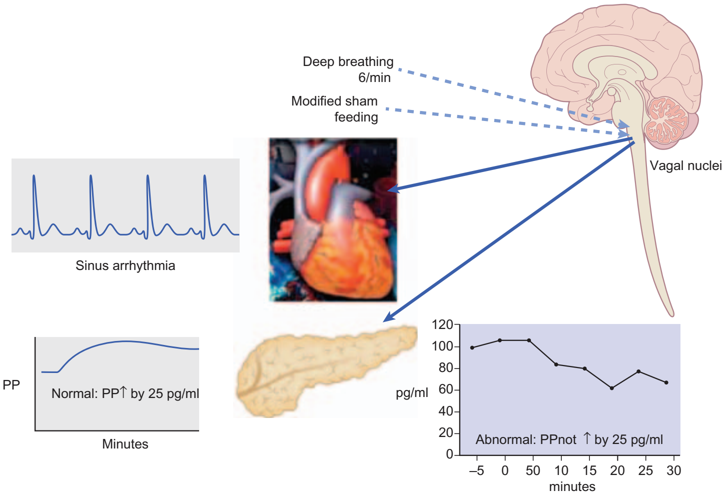
Deep breathing 6/min
Modified sham feeding
Vagal nuclei
Sinus arrhythmia
PP
Normal: PP↑ by 25 pg/ml
Minutes
pg/ml
120
100
80
60
40
20
0
Abnormal: PPnot ↑ by 25 pg/ml
–5
0
50
10
15
20
25
30
minutes

FIGURE 14-6 ■ Assessment of thoracic vagal function by documentation of sinus arrhythmia and abdominal vagal function by the plasma pancreatic polypeptide (PP) response to modified sham feeding by chewing and spitting a bacon-and-cheese toasted sandwich.

MANAGEMENT OF GASTROINTESTINAL MOTILITY DISORDERS

The principles of management of any gastrointestinal motility disorder are restoration of hydration and nutrition by the oral, enteral, or parenteral route; suppression of bacterial overgrowth (e.g., with oral tetracycline); use of prokinetic agents or stimulant laxatives; and resection of localized disease. An update of pharmacotherapy is provided elsewhere.

Pyridostigmine (usually 30 to 60 mg taken four times daily, with escalation up to maximum 360 mg per day) has been used to treat autoimmune neuropathy causing dysmotility or diabetic neuropathy with constipation. Oral pyridostigmine accelerates colonic transit and improves bowel function in diabetic patients with chronic constipation and is also used (liquid formula) for gastroparesis.

The role of surgery for motility disorders due to neurologic disease is restricted to those patients with intractable colonic or rectal symptoms, particularly incontinence. There is no good rationale for vagotomy or for partial or total gastrectomy in patients with chronic neuropathies causing gastric stasis. In patients with severe colonic inertia, subtotal colectomy with ileorectostomy is usually successful, but this treatment has been used only rarely in patients with neurologic or muscle disease. Surgery for local complications of severe constipation may be necessary, as in patients with rectal intussusception or prolapse.

A Cochrane systematic review of the management of fecal incontinence and constipation in adults with central neurologic diseases12 concluded that it was not possible to make any recommendations, and bowel management remains empirical.

CONCLUDING COMMENTS

Gastrointestinal motor abnormalities result when extrinsic nerves are disturbed and are unable to modulate the motor functions of the digestive tract, which depend on the enteric nervous system and the automaticity of the smooth muscles. Disorders at all anatomic levels of the extrinsic neural control system and degenerations of gut smooth muscle have been reported in association with gut motor dysfunction and illustrate the important role of the nervous system in the etiology of gastrointestinal symptoms. Although much emphasis in the literature is placed on dysphagia and constipation in neurologic disorders, more recent studies have highlighted incontinence, vomiting, and abdominal distention in the symptomatology of such patients. Strategies that evaluate the physiologic functions of the digestive tract and the function and structure of the autonomic nervous system are available and aid in the selection of rational therapies for patients, including physical and biofeedback training (e.g., for dysphagia or incontinence), prokinetic agents (for neuropathic forms of gastroparesis, intestinal pseudo-obstruction, or slow-transit colonic disorders), and nutritional support using the enteral or parenteral route. Electric or magnetic stimulation of lumbar sacral roots may alleviate certain symptoms, such as constipation in paraplegics.

ACKNOWLEDGMENT

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CHAPTER

15

Neurologic Manifestations of Nutritional Disorders

BRENT P. GOODMAN

VITAMIN B_{12} DEFICIENCY
  Etiology
  Clinical Manifestations
  Diagnosis
  Treatment
FOLATE DEFICIENCY
  Etiology
  Clinical Manifestations
  Diagnosis
  Treatment
COPPER DEFICIENCY
  Etiology
  Clinical Manifestations
  Diagnosis
  Treatment
VITAMIN E DEFICIENCY
  Etiology
  Clinical Manifestations
  Diagnosis
  Treatment
THIAMINE (VITAMIN B_1) DEFICIENCY
  Etiology
  Clinical Manifestations
    Beriberi
    Wernicke Encephalopathy
    Korsakoff Syndrome
  Diagnosis
  Treatment
PYRIDOXINE (B_6) DEFICIENCY
  Etiology
  Clinical Manifestations
  Diagnosis
  Treatment
NIACIN DEFICIENCY
  Etiology
  Clinical Manifestations
  Diagnosis and Treatment
VITAMIN A DEFICIENCY
  Etiology
  Clinical Manifestations
  Diagnosis and Treatment
VITAMIN D DEFICIENCY
  Etiology
  Clinical Manifestations
  Diagnosis and Treatment

LATHYRISM
KONZO

Maintenance of medical and neurologic health requires adequate ingestion, absorption, and storage of vitamins and minerals. Nutritional deficiencies may result from inadequate intake or malabsorption of critical vitamins and micronutrients. Individuals at risk for deficient nutrient intake include the impoverished in developed and underdeveloped countries (where certain nutritional disorders may be endemic), individuals with eating disorders or engaging in fad or restrictive diets, those suffering from chronic alcoholism, and patients with chronic medical conditions that result in malabsorption or require prolonged parenteral nutrition. Malabsorption may result from gastrointestinal surgery, including bariatric surgery for obesity, and from chronic gastrointestinal disorders such as celiac disease, Whipple disease, bacterial overgrowth, and inflammatory bowel disease. Excessive ingestion of certain substances, including vitamins and micronutrients, may result in neurologic impairment directly (vitamin B_6 excess) or indirectly by interfering with absorption of certain vitamins (copper deficiency induced by hyperzincemia). Awareness of the characteristic clinical features of the various nutritional disorders and conditions associated with them facilitates more timely recognition and treatment, and directly impacts prognosis (Table 15-1).

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TABLE 15-1 ■ Nutritional Disorders–Diagnosis and Treatment

Vitamin	Diagnosis	Treatment
Vitamin B_{12} deficiency	Serum cobalamin Serum methylmalonic acid Serum homocysteine	Intramuscular vitamin B_{12} 1000 μg × 5 days; once monthly thereafter or vitamin B_{12} 1,000 μg daily orally
Nitrous oxide	Serum cobalamin (rendered inactive by N_2O)	Cessation of nitrous oxide exposure; Intramuscular vitamin B_{12}; Oral methionine considered
Folate deficiency	Serum folate, homocysteine	Oral folate 1 mg tid initially; then 1 mg daily thereafter
Copper deficiency	Serum copper, ceruloplasmin; urinary copper	Discontinue zinc; oral copper 8 mg daily for 1 week; 6 mg daily for 1 week; 4 mg daily for 1 week; 2 mg daily thereafter
Vitamin E	Serum vitamin E; ratio serum vitamin E to serum lipids Cholesterol, triglycerides	Vitamin E–dose range 200 mg–200 mg/kg/day oral or intramuscular
Thiamine	Clinical diagnosis; brain MRI	Thiamine 100 mg IV followed by 50–100 mg IV/IM until nutritional status stable
Pyridoxine	Serum pyridoxal phosphate	Pyridoxine 50–100 mg daily
Niacin	Urinary excretion niacin metabolites	Nicotinic acid 25–50 mg oral/IM

As is true with the evaluation of all suspected neurologic disorders, the identification of nutritional deficiencies requires a careful neurologic history and examination. A meticulous review of medication history, including prescription and over-the-counter medications, is necessary. Certain prescription and nonprescription medications may increase an individual's risk of developing a vitamin deficiency (e.g., histamine H2 blockers and vitamin B_{12} deficiency), and excessive ingestion of particular supplement medications may result in vitamin malabsorption (e.g., zinc-induced copper deficiency) and deficiency. A careful review of past medical and surgical history is critical, as a prior history of gastric bypass surgery, inflammatory bowel disease, celiac disease, and other medical and surgical conditions may compromise nutritional status. It is also essential in the evaluation of such patients to understand the time course over which various vitamin deficiencies may develop. For example, body stores of thiamine are limited, and thiamine deficiency may develop within weeks, whereas cobalamin (vitamin B_{12}) deficiency develops over years. Additionally, the identification of a particular vitamin deficiency should prompt a thorough laboratory evaluation for other vitamin deficiencies, as multiple vitamin deficiencies may occur in the same patient.

VITAMIN B_{12} DEFICIENCY

Vitamin B_{12} (cobalamin) deficiency is a common condition, with estimated prevalence rates ranging from 2 to 15 percent of the elderly, depending upon the population studied and diagnostic criteria used. Despite these high prevalence rates, there remains no consensus on how to diagnose and evaluate patients with suspected vitamin B_{12} deficiency. Recognition of vitamin B_{12} deficiency is critical, as the hematologic and neurologic manifestations are potentially reversible if diagnosed and treated in a timely manner. However, if treatment is initiated too late, the neurologic impairment resulting from vitamin B_{12} deficiency may be irreversible.

Vitamin B_{12} is a cofactor for the enzymes methionine synthase and L-methylmalonyl-coenzyme A mutase and is required for proper red blood cell formation, normal neurologic function, and DNA synthesis. Vitamin B_{12} is necessary for the initial myelination, development, and maintenance of myelination within the central nervous system. Classically, vitamin B_{12} deficiency results in a myelopathy, or "subacute combined degeneration," which results from demyelination of the posterolateral columns of the cervical and thoracic spinal cord.[1] Demyelination of cranial nerves, peripheral nerves, and brain may also occur and has been referred to as "combined-systems disease." Vitamin B_{12} deficiency may result in megaloblastic anemia, with macrocytosis, anisocytosis, hypersegmented neutrophils, leukopenia, thrombocytopenia, or pancytopenia.

Etiology

Vitamin B_{12} is a water-soluble vitamin that exists in several forms, all of which contain cobalt, and are collectively referred to as cobalamins. Methylcobalamin and 5-deoxyadensoylcobalamin are the forms of

TABLE 15-2 ■ Risk Factors for Vitamin B_{12} Deficiency
Pernicious anemia
Atrophic gastritis
Achlorhydria-induced food-cobalamin malabsorption
Partial gastrectomy
Ileal resection
Bariatric surgery
Histamine-2 (H2) receptor antagonists
Proton pump inhibitors
Glucophage
Bacterial overgrowth
Pancreatic disease
Celiac disease
Helicobacter pylori infection
Diphyllobothrium latum infection
Nitrous oxide
Dietary restriction

vitamin B_{12} that are active in human metabolism. Vitamin B_{12} is contained in a number of animal proteins, in fortified breakfast cereals, and in some nutritional yeast products. Daily losses of vitamin B_{12} are minimal, and even in cases of severe malabsorption, it may take 5 years or more to develop symptomatic vitamin B_{12} deficiency.

Vitamin B_{12} deficiency in elderly patients most commonly results from pernicious anemia, atrophic gastritis, and achlorhydria-induced cobalamin malabsorption[2,3] (Table 15-2). The incidence of atrophic gastritis increases with age and may at least partially explain the increased frequency of vitamin B_{12} deficiency with aging. Achlorhydria results in impaired extraction of vitamin B_{12} from food sources. Partial gastrectomy, bariatric surgery, and ileal resection may result in the malabsorption of vitamin B_{12}, and partial gastrectomy has been associated with loss of intrinsic factor. Gastroenterologic disorders such as celiac disease, Crohn disease, ileitis, pancreatic disease, and bacterial overgrowth may also result in vitamin B_{12} deficiency. Certain medications, such as histamine (H2) blocking agents, proton pump inhibitors, and glucophage may also increase one's risk of developing vitamin B_{12} deficiency. Vitamin B_{12} deficiency rarely results from inadequate intake in vegetarians and would be expected to develop only after many years.

Nitrous oxide alters the cobalt core of cobalamin, converting it into an inactive, oxidized form. Hence, nitrous oxide abuse may result in cobalamin deficiency, with most reported cases associated with low or borderline-low vitamin B_{12} levels. A single exposure to nitrous oxide may be enough to precipitate neurologic impairment in an individual with unsuspected vitamin B_{12} deficiency, with time to symptom onset ranging from immediate postexposure up to 2 months. Nitrous oxide remains one of the more commonly used anesthetic agents worldwide, and can also be obtained for abuse in the form of whipped cream canisters, and as "whippets," which are small bulbs containing nitrous oxide.

Clinical Manifestations

Neurologic signs and symptoms of vitamin B_{12} deficiency may be the initial manifestation of this condition. Paresthesias and ataxia are the most common initial symptoms in patients with vitamin B_{12} deficiency. Classically, vitamin B_{12} deficiency results in a myelopathy, which may be accompanied by a peripheral neuropathy. The myelopathy results from impairment in posterior column and lateral spinothalamic tract function, with a combination of pyramidal signs and posterior column sensory loss evident on examination. The peripheral neuropathy associated with vitamin B_{12} deficiency is typically mild and is predominantly axonal on electrodiagnostic testing.

Neuropsychiatric manifestations range from memory impairment, change in personality, delirium, and even psychosis. Optic neuropathy, resulting in diminished visual acuity, optic atrophy, and centrocecal scotomas may be seen. Symptoms of orthostatic intolerance, resulting from orthostatic hypotension, are an uncommon manifestation of vitamin B_{12} deficiency. Other much less commonly encountered neurologic conditions attributed to vitamin B_{12} deficiency include cerebellar ataxia, orthostatic tremor, ophthalmoplegia, and vocal cord paralysis. A number of constitutional symptoms may accompany the neurologic signs and symptoms, including fatigue, weight loss, fever, dyspnea, and gastrointestinal symptoms.

Diagnosis

Serum cobalamin is the initial screening test in patients with suspected vitamin B_{12} deficiency (Table 15-1), however limitations in cobalamin sensitivity must be recognized. Some patients with vitamin B_{12} deficiency will have normal cobalamin levels. In patients with borderline low cobalamin levels, and particularly in those patients strongly suspected of vitamin B_{12} deficiency, methylmalonic acid and homocysteine levels should be checked. Methylmalonic acid and homocysteine levels are increased in as many as one-third of patients with low-normal serum cobalamin levels and vitamin B_{12} deficiency. However, these tests, particularly homocysteine, lack specificity (Table 15-2).

Once a diagnosis of vitamin B_{12} deficiency is established, diagnostic testing may be pursued in order to determine the cause. Antibodies to intrinsic factor are seen in only 50 to 70 percent of patients with pernicious anemia, but are highly specific. Antiparietal cell antibodies lack sensitivity and specificity and have limited utility. Gastrin antibodies are 70 percent sensitive and specific for pernicious anemia. Elevated serum gastrin and decreased pepsinogen I levels have been reported to be abnormal in 80 to 90 percent of patients with pernicious anemia, but the specificity of these tests may be limited. The Schilling test is rarely utilized presently due to concerns about radiation exposure, cost, and diagnostic accuracy.

Nerve conduction studies (NCSs) and needle electromyography (EMG) may confirm the presence of an axonal sensorimotor peripheral neuropathy. Somatosensory evoked potentials (SEPs) may show slowing in central proprioceptive pathways. Brain and spinal cord magnetic resonance imaging (MRI) studies may show signal change in subcortical white matter and in posterolateral columns.

Treatment

Treatment of neurologic impairment due to vitamin B_{12} deficiency involves the administration of high-dose oral, sublingual, or intramuscular cobalamin. With malabsorption, 1000 μg of cobalamin is administered intramuscularly for 5 days and monthly thereafter. There is evidence to suggest that 1000 μg of oral or sublingual cobalamin, given daily, is as effective as intramuscular administration.[4] Lifelong vitamin B_{12} supplementation therapy is typically necessary, unless a potentially reversible cause is identified and treated. Hematologic recovery occurs within the first 1 to 2 months and is complete. The neurologic condition should stabilize and improvement may occur over the first 6 to 12 months following the initiation of treatment. Neurologic recovery may be incomplete, particularly in those with significant neurologic deficits prior to the initiation of therapy. Methylmalonic acid and homocysteine levels should be utilized to monitor response to therapy, and typically should normalize within 10–14 days.

Patients with pernicious anemia should undergo endoscopy, as they are at higher risk of developing gastric and carcinoid cancers. Upper endoscopy should be considered in other patients as well, including those with other gastrointestinal symptoms and those with other concomitant vitamin deficiencies.

FOLATE DEFICIENCY

The active form of folate, tetrahydrofolic acid (THFA), is essential in the transfer of one-carbon units to substrates utilized in the synthesis of purine, thymidine, and amino acids. Methyl tetrahydrofolate (THF) is required for the cobalamin-dependent remethylation of homocysteine to methionine, and methylene THF methylates deoxyuridylate to thymidylate. While folate deficiency might be expected to result in similar complications as vitamin B_{12} deficiency, neurologic manifestations of isolated folate deficiency are extremely uncommon.

Etiology

Folate is present in animal products, citrus fruits, and green, leafy vegetables. Normal body stores of folate range from 500 to 20,000 μg, and 50 to 100 μg are required daily. Serum folate falls within 3 weeks of diminished intake or malabsorption, and clinical signs of folate deficiency may occur within months. After ingestion, folate polyglutamates undergo hydrolysis to monoglutamates, which are absorbed in the proximal small intestine and ileum. Absorbed folate monoglutamates are then metabolized by the liver to 5-methyl-tetrahydrofolate (MTHF), the principal circulating form of folate. The cellular uptake of MHTF is mediated by four different carrier systems: a proton-coupled folate transporter, low-affinity high-capacity reduced folate carrier, and two high-affinity folate receptors.

Folate deficiency is one of the more common nutritional disorders worldwide. Risk factors for folate deficiency include malnutrition, conditions associated with increased folate requirements (e.g., pregnancy, lactation, and chronic hemolytic anemia), gastroenterologic disorders, and certain medications (Table 15-3). Gastroenterologic conditions that affect folate absorption in the small bowel may result in folate deficiency, including tropical sprue, celiac disease, bacterial overgrowth syndrome, inflammatory bowel disease, and pancreatic insufficiency. Gastric surgeries or medications that reduce gastric secretions may also result in folate deficiency. A number of other medications, such as methotrexate, aminopterin, pyrimethamine, trimethoprim, and triamterene, inhibit dihydrofolate reductase and may result in folate deficiency. Mechanisms by which other medications such as anticonvulsants, sulfasalazine, oral contraceptives, and antituberculous drugs affect folate levels have not been established.

Eight inborn errors of folate absorption have been described, including hereditary folate malabsorption, cerebral folate transporter deficiency, glutamate formiminotransferase deficiency, severe methylenetetrahydrofolate reductase (MTHFR) deficiency, dihydrofolate reductase deficiency, methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) protein deficiency, and functional methionine synthase deficiency. Clinical manifestations of these disorders may include megaloblastic anemia, mental retardation, seizures, movement disorders, and peripheral neuropathy. Early identification and treatment with folate may result in clinical improvement in certain forms of these disorders. Methylenetetrahydrofolate deficiency is the most common of these disorders, with variable neurologic and vascular manifestations, including mental retardation, seizures, motor and gait disorders, schizophrenia, and thromboses, with laboratory studies showing hyperhomocysteinemia and homocystinuria.

TABLE 15-3 ■ Causes of Folate Deficiency

Malnutrition (e.g., in alcoholism, premature infants, adolescents)
Increased folate requirement (e.g., pregnancy, lactation, chronic hemolytic anemia)
Dietary restriction (e.g., phenylketonuria)
Malabsorption (e.g., tropical sprue, celiac disease, bacterial overgrowth, inflammatory bowel disease, giardiasis)
States of reduced gastric secretions (e.g., gastric surgery, atrophic gastritis, H2 receptor antagonists, proton pump inhibitors, treatment of pancreatic insufficiency)
Medications that inhibit dihydrofolate reductase (e.g., aminopterin, trimethoprim, methotrexate, pyrimethamine, triamterene)
Medications with unclear mechanism (e.g., anticonvulsants, antituberculous drugs, sulfasalazine, oral contraceptive agents)
Inborn errors of folate metabolism (e.g., hereditary folate malabsorption, cerebral folate transporter deficiency, glutamate formiminotransferase deficiency, severe methylenetetrahydrofolate reductase (MTHFR) deficiency, dihydrofolate reductase deficiency, methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) protein deficiency, functional methionine synthase deficiency)

Clinical Manifestations

Maternal folate deficiency during or around the time of conception has been reported to result in more than 50 percent of neural tube defects.[5] Myeloneuropathy, peripheral neuropathy, and megaloblastic anemia have been associated with folate deficiency. These potential manifestations of folate deficiency are clinically indistinguishable from those of vitamin B_{12} deficiency, although as previously mentioned they are much less common. Preliminary reports suggest that folate deficiency may be associated with an increased risk of peripheral vascular disease, coronary artery disease, cerebrovascular disease, and cognitive impairment, although these preliminary reports await further confirmatory research.

Diagnosis

Serum folate, red blood cell folate, and homocysteine levels may be used to evaluate an individual with suspected folate deficiency. Results depend upon methods and laboratories where these studies are performed. Serum folate levels fluctuate considerably and do not always accurately reflect tissue stores. Red blood cell folate levels may more accurately predict tissue stores, but there is considerable laboratory assay variability. Homocysteine levels have been demonstrated to be elevated in 86 percent of patients with clinically significant folate deficiency. Typically, a serum folate level of 2.5 μg/L has been utilized as the cutoff for folate deficiency; however, it has been suggested that a range of 2.5 to 5 ng/mL may reflect mildly compromised folate status.[6]

Treatment

Vitamin B_{12} levels should also be assessed with suspected folate deficiency, and if low, vitamin B_{12} supplementation should be initiated immediately. Oral administration of folic acid may be adequate, typically 1 mg three times daily followed by maintenance dosing of 1 mg daily. Parenteral administration of folic acid may be considered in acutely ill patients, and particularly in patients with malabsorption. Folate supplementation, 0.4 mg daily, is recommended in women of childbearing age with epilepsy.

COPPER DEFICIENCY

Copper is a trace element involved in a number of metalloenzymes, critical in the development and maintenance of nervous system structure and function. These enzymes include cytochrome c-oxidase (electron transport, oxidative phosphorylation), copper/zinc superoxide dismutase (antioxidant defense), tyrosinase (melanin synthesis), dopamine β-hydroxylase (catecholamine synthesis), lysl oxidase (cross-linking collagen and elastin), and others.

Copper deficiency in animals was first recognized in sheep in 1937, manifesting as an enzootic ataxia (also known as swayback), and then subsequently was noted to affect other animals similarly.[7] Hematologic abnormalities were the first signs of acquired copper deficiency recognized in humans, with anemia, neutropenia, and sideroblastic anemia evident in some but not all patients with copper deficiency. The neurologic manifestations of acquired copper deficiency have been defined over the past several years.

Etiology

Copper is present in a wide variety of foods, with shellfish, oysters, legumes, organ meats, chocolate, nuts, and whole-grain products being particularly rich in copper. The estimated daily requirement for copper is 0.70 mg, and the estimated total body copper content is 50 to 120 mg. Copper absorption occurs in the stomach and proximal small intestine via active and passive transport processes. The Menkes P-type ATPase (ATP7A) is responsible for copper efflux from enterocytes.

Malabsorption following prior gastric surgery and excessive, exogenous zinc ingestion are the most frequently identified causes of symptomatic copper deficiency. Copper deficiency may also occur in premature, low-birthweight, and malnourished infants, and may occur as a complication of total parenteral or enteral nutrition. Chronic gastrointestinal conditions such as celiac disease, cystic fibrosis, inflammatory bowel disease, and bacterial overgrowth may result in copper malabsorption. Patients should be queried about the use of zinc supplements, including denture creams, some of which have excessive zinc and may induce copper deficiency. Excessive zinc ingestion may also cause copper deficiency. It is hypothesized that excessive zinc ingestion upregulates intestinal enterocyte metallothionein production, which has a higher affinity for copper than zinc, resulting in retention of copper in intestinal enterocytes and loss of copper in the stool. Some patients will not have any identifiable cause for copper deficiency.

Menkes disease is a congenital disorder with clinical signs and symptoms that result from copper deficiency. This condition results from a mutation in the *ATP7A* gene, which leads to failure of intestinal copper transport across the gastrointestinal tract and subsequent copper deficiency. Wilson disease is a disorder of copper toxicity that results from an impairment in biliary copper excretion.

Clinical Manifestations

Hematologic abnormalities have been well described in copper deficiency, and include anemia and neutropenia, primarily. Failure to recognize hematologic derangements as resulting from copper deficiency has led to misdiagnoses such as myelodysplastic syndrome, aplastic anemia, and sideroblastic anemia. Patients with copper deficiency may develop a myeloneuropathy that resembles the syndrome of subacute combined degeneration associated with vitamin B_{12} deficiency. Pyramidal signs, such as brisk deep tendon reflexes at the knees, and extensor plantar responses are typically present, along with impairment in posterior column sensory modalities. Sensory loss is characteristically severe, and frequently leads to a sensory ataxia. Neuropathic extremity pain may be reported, and distal lower limb weakness and atrophy may develop suggesting peripheral nerve involvement.

Diagnosis

Low serum copper and ceruloplasmin levels establish the diagnosis of copper deficiency. Twenty-four-hour urine copper levels will often be decreased, in contrast to an elevation in urinary copper seen with Wilson disease. Serum and 24-hour urine zinc levels should also be assessed. Ceruloplasmin is an acute-phase reactant and may be increased in various conditions, including pregnancy, oral contraceptive use, liver disease, malignancy, hematologic disease, smoking, diabetes, uremia, and other inflammatory and infectious diseases. In the presence of these conditions, copper deficiency may be masked. Serum copper and ceruloplasmin may be decreased in Wilson disease, hence laboratory evidence of copper deficiency does not necessarily indicate copper deficiency in the absence of clinical features consistent with the diagnosis.

Cervical MRI studies may show T2 hyperintensity involving the dorsal columns (Fig. 15-1). Somatosensory evoked potentials often show slowing in central proprioceptive pathways, and NCS and needle EMG demonstrate findings consistent with an axonal sensorimotor peripheral neuropathy. Brain MRI studies may show diffuse T2 hyperintensities involving the subcortical white matter, suggesting demyelination.

Treatment

Treatment of copper deficiency involves discontinuation of zinc in those with excessive zinc consumption as well as copper supplementation. A recommended regimen is 8 mg of orally administered elemental copper administered daily for 1 week, followed by 6 mg daily for the next week, 4 mg daily during the third week, and 2 mg daily thereafter. Occasionally intravenous copper supplementation is necessary. Ongoing copper supplementation may not be necessary in patients with copper deficiency due to zinc excess (with cessation of zinc ingestion) or in those with a treatable gastrointestinal condition resulting in copper malabsorption (such as celiac disease). Patients without an identifiable cause of copper deficiency or those with copper malabsorption due to gastric bypass surgery typically require lifelong copper supplementation.

Similar to vitamin B_{12} deficiency, the hematologic abnormalities associated with copper deficiency normalize within 1 month of copper repletion. Neurologic deficits are expected to stabilize, but there may be little improvement in neurologic signs and symptoms, particularly in those with more severe neurologic impairment.

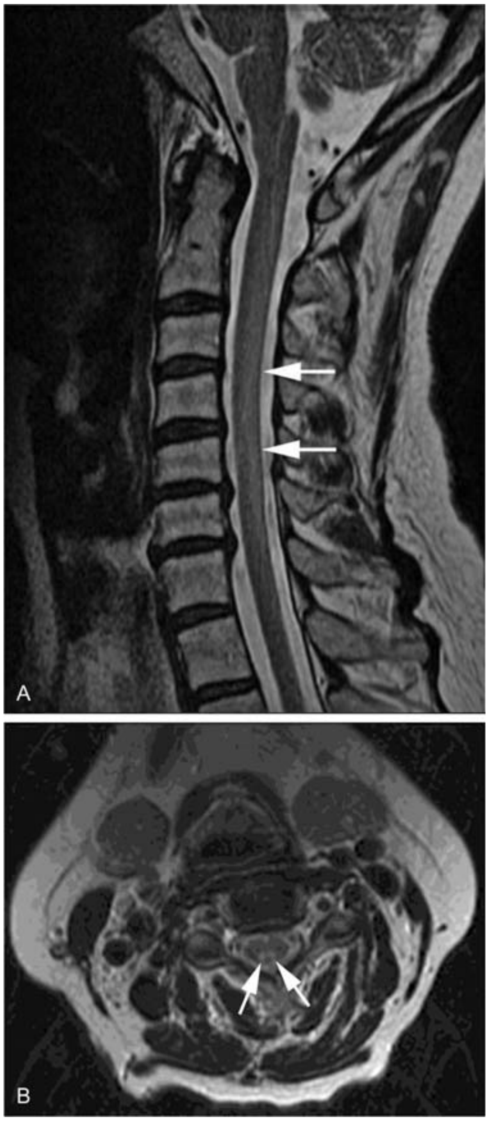

FIGURE 15-1 ■ Cervical magnetic resonance imaging (MRI) in a patient with copper deficiency myeloneuropathy. T2 hyperintensity demonstrated in posterior columns in *A*, sagittal and *B*, axial images (*arrows*). (From Goodman BP, Chong BW, Patel AC, et al: Copper deficiency myeloneuropathy resembling B_{12} deficiency: partial resolution of MR imaging findings with copper supplementation. AJNR Am J Neuroradiol 27:2112, 2006, with permission.)

VITAMIN E DEFICIENCY

Vitamin E is a fat-soluble vitamin with important antioxidant properties, providing protection against oxidative stress and inhibiting the fatty acid peroxidation of membrane phospholipids. Vitamin E refers to a family of tocopherols and tocoretinols, of which α-tocopherol is the most abundant and active biologic form of vitamin E in the human diet.

Etiology

Nut oils, sunflower seeds, whole grains, wheat germ, and spinach are foods high in vitamin E. Vitamin E absorption requires bile salts and pancreatic esterases. Vitamin E is incorporated into chylomicrons in intestinal enterocytes, and upon release into the circulation lipolysis ensues, resulting in the transfer of vitamin E to high-density and other lipoproteins. Alpha-tocopherol transfer protein in the liver is responsible for the incorporation of vitamin E into very-low-density lipoprotein (VLDL), which also delivers vitamin E to tissues.

Vitamin E absorption requires pancreatic and biliary secretions, and may therefore result from chronic cholestasis and pancreatic insufficiency. Chronic total parenteral nutrition (TPN) with inadequate vitamin E supplementation may be a cause. Other gastrointestinal disorders may result in vitamin E malabsorption, including celiac disease, inflammatory bowel disease, blind loop syndrome, bacterial overgrowth, irradiation, and cystic fibrosis. Genetic causes of vitamin E deficiency include ataxia with vitamin E deficiency resulting from α-tocopherol transport protein (α-TTP) deficiency, apolipoprotein B mutation (homozygous hypobetalipoproteinemia), or a defect in the microsomal triglyceride transfer protein (abetalipoproteinemia).

Clinical Manifestations

Numerous neurologic manifestations of vitamin E deficiency have been reported including ophthalmoplegia, retinopathy, and a spinocerebellar syndrome with an associated peripheral neuropathy, resembling Friedreich ataxia. This spinocerebellar syndrome manifests with signs of a cerebellar ataxia, posterior column sensory loss, pyramidal signs, and sensory loss on neurologic examination. A myopathy has been associated with vitamin E deficiency, with reported pathologic features including inflammatory infiltrates and rimmed vacuoles. Vitamin E deficiency has rarely been associated with a demyelinating neuropathy.

Diagnosis

Low serum vitamin E levels confirm the diagnosis of vitamin E deficiency. Serum lipids, cholesterol, and VLDL affect serum vitamin E levels, and serum vitamin E levels can be corrected for these factors by dividing serum vitamin E levels by the sum of serum triglycerides and cholesterol. Increased stool fat and decreased serum carotene levels may also be noted in patients with fat malabsorption.

Spinal MRI studies may show T2 signal change in the dorsal columns, similar to what is seen with vitamin B_{12} and copper deficiency. Median and tibial SEPs may show slowing in central proprioceptive pathways.

Treatment

Vitamin E supplementation utilizing dosages ranging from 200 mg/day to 200 mg/kg/day are administered. Parenteral administration may be necessary with some conditions, particularly those with severe malabsorption. Unless there is a reversible cause for vitamin E deficiency, lifelong supplementation may be necessary.

THIAMINE (VITAMIN B_1) DEFICIENCY

The active form of thiamine is thiamine pyrophosphate (TPP), which functions as a coenzyme in the metabolism of carbohydrates, lipids, and branched chain amino acids. It is involved in decarboxylation of α-keto acids during adenosine triphosphate (ATP) synthesis and maintenance of reduced glutathione in erythrocytes. TPP additionally is a coenzyme in myelin synthesis, and has been hypothesized to play a role in cholinergic and serotonergic neurotransmission through effects on sodium channel function.

Etiology

Thiamine, or vitamin B_1, is a water-soluble vitamin most commonly found in unrefined cereal grains, wheat germ, yeast, soybean flour, and pork. A water-soluble vitamin, storage (hepatic) of thiamine is minimal, with excess excreted in the urine. This and the 10- to 14-day half-life necessitate regular dietary supply of thiamine to prevent deficiency. The recommended daily allowance ranges from 1.0 to 1.5 mg/day, but requirements increase in proportion to carbohydrate intake and metabolic rate.

Thiamine is converted in the jejunum to TPP and absorbed throughout the small intestine, passing through the portal circulation prior to active and passive transport across the blood–brain barrier. Hepatic storage is minimal and the half-life of thiamine is short, leading to clinical manifestations of deficiency within days of depletion or reduced stores.

With thiamine supply being intake-dependent, deficiency is seen in persons with compromised nutritional status: reduced intake (e.g., alcoholism, starvation, fad dieting and dieting aids, chronic illness, inadequate parenteral nutrition, thiaminase-containing foods); malabsorption (e.g., bariatric surgery, gastrointestinal/liver/pancreatic disease, excess antacid use); and increased losses (persistent emesis or diarrhea, renal failure with dialysis) can result in clinical deficiency (Table 15-4). Deficiency is also seen from increased thiamine requirements such as in high metabolic states (e.g., pregnancy, critical illness, hyperthyroidism, malignancy, infection) and high carbohydrate intake (e.g., intravenous glucose administration, refeeding syndrome, parenteral nutrition). In the latter case, the demand for thiamine, which is needed for glucose oxidation, exceeds replacement.

In developed countries thiamine deficiency is seen most commonly with excessive alcohol use, although the rise of fad dieting and bariatric surgery has led to an increasing incidence in nonalcoholics. Inadequate intake, reduced gastrointestinal absorption, impaired conversion to active metabolite, increased demand (for carbohydrate metabolism), and reduced hepatic storage of thiamine all contribute to the development of clinical deficiency in alcoholics. Genetic polymorphisms in thiamine and alcohol metabolism may predispose to the development of a thiamine deficiency syndrome.

Clinical Manifestations

Thiamine is a key cofactor in carbohydrate metabolism, acting as a coenzyme in the tricarboxylic acid cycle and hexose monophosphate shunt. Deficiency results in a reduction of high-energy phosphates with lactic acid accumulation and impaired oxygen uptake. Cerebral tissue is dependent on glucose for energy and is particularly vulnerable to damage from impaired glucose metabolism. Neurotoxicity is thought to result from disruption in osmotic gradients, glutamate accumulation, and impaired blood–brain barrier permeability. Animal models have shown a predilection for brainstem and cerebellar involvement.

Thiamine deficiency most commonly affects the heart and both central and peripheral nervous systems. Three well-described manifestations include beriberi (dry and wet), infantile beriberi, and Wernicke encephalopathy with Korsakoff syndrome.

TABLE 15-4 ■ Causes of Thiamine Deficiency

Reduced intake
- Alcoholism
- Starvation
- Fad dieting/dieting aids
- AIDS
- Inadequate parenteral nutrition
- Thiaminase-containing foods (polished rice, overbaked bread, prolonged milk pasteurization)

Malabsorption
- Bariatric surgery
- Gastrointestinal/hepatic/pancreatic disease
- Antacids

Increased loss
- Persistent emesis
- Persistent diarrhea
- Renal failure/dialysis

High metabolic state
- Pregnancy
- Critical illness
- Hyperthyroidism
- Malignancy
- Infection
- Chemotherapy (ifosfamide)

Increased carbohydrate intake
- Intravenous glucose administration
- Refeeding syndrome
- Parenteral nutrition

AIDS, acquired immunodeficiency syndrome.

BERIBERI

Thiamine deficiency is classically described as a painful, length-dependent sensorimotor axonal neuropathy. In malnourished individuals, concomitant deficiency in other B vitamins such as pantothenic acid and pyridoxine may also contribute to the development of a nutritional polyneuropathy. Fatigue, irritability, and muscle cramps may be the earliest manifestation, presenting within days to weeks of deficiency. Symptoms can be rapidly progressive and evolve from distal sensory loss or burning dysesthesias to muscle weakness. Cranial neuropathy and recurrent laryngeal nerve palsy have been described, and an autonomic neuropathy may also be present.

Dry beriberi refers to the presence of a polyneuropathy, while wet beriberi is used when the development of high-output cardiac failure and peripheral edema predominate. They are considered clinical spectra of the same disease process, with the potential of one to evolve into the other.

Infantile beriberi is seen in infants with thiamine-deficient diets, including breast-fed children of thiamine-deficient mothers. The clinical spectrum is varied and may involve the development of cardiac, ophthalmologic, central nervous system, and systemic abnormalities. Infants can present with irritability, vomiting, diarrhea, failure to thrive, seizures, ophthalmoplegia, drowsiness, and respiratory difficulty.

WERNICKE ENCEPHALOPATHY

Wernicke encephalopathy refers to a syndrome characterized by varying degrees of subacute gait and trunk ataxia, ocular abnormalities, and mental status changes. The presentation is heterogeneous and autopsy studies suggest it often goes undiagnosed. Ataxia is caused primarily by cerebellar dysfunction and can be accompanied by other localizing abnormalities such as dysarthria and dysmetria. Vestibular dysfunction and co-existing neuropathy can contribute to the development of ataxia. Ocular manifestations are many and include nystagmus, ophthalmoparesis, pupillary abnormalities, and decreased visual acuity. Delirium, somnolence, impaired attention, and lack of orientation are prominent cognitive manifestations of this syndrome. Brainstem or hypothalamic involvement in addition to comorbid autonomic neuropathy may result in fluctuations in body temperature, blood pressure, and heart rate. Typically, pathologic changes are most prominent in the mammillary bodies.

KORSAKOFF SYNDROME

Approximately 80 percent of patients with Wernicke encephalopathy develop residual Korsakoff syndrome, an amnestic condition characterized by severe retrograde and anterograde memory loss and subsequent confabulation. The dorsal medial nucleus of the thalamus is often affected. Involvement of the limbic and frontal cortex has been implicated in the development of anterograde and retrograde amnesia, respectively. Memory impairments are often chronic and progressive.[8]

Diagnosis

Thiamine deficiency remains a clinical diagnosis; urine and serum thiamine levels are not reflective of tissue thiamine concentrations and can often be normal.[9] Surrogate measurements can include erythrocyte thiamine diphosphate levels or the transketolase activation assay, but they must be drawn prior to treatment initiation due to rapid normalization. Impaired aerobic metabolism can cause elevations in lactate and subsequent anion-gap metabolic acidosis. Brain MRI can show T2 signal abnormalities in paraventricular regions including the thalamus, hypothalamus, mammillary bodies, periaqueductal midbrain,pons, medulla, and cerebellum (Fig. 15-2). Reversible contrast enhancement of the mammillary bodies is often seen in Wernicke encephalopathy. Development of vasogenic edema may cause diffusion-weighted abnormalities, often resolving with treatment. MR spectroscopy can show elevation in cerebral lactate but is not commonly used.

Treatment

Parenteral thiamine replacement is the mainstay of treatment, but must be administered to high-risk patients prior to glucose or TPN infusion. Glucose oxidation is highly thiamine-dependent and inadequate supplementation can result in intracellular shift of already-depleted thiamine stores and resultant neurotoxicity. Ongoing poor nutritional status often necessitates oral maintenance therapy at 50 to 100 mg daily. Attention should be given to the possibly emergent underlying cause of malnutrition or increased metabolic demand such as sepsis.

Clinical manifestations of thiamine deficiency are partially reversible with treatment; heart failure, ocular abnormalities, and acute mental status changes often resolve quickly. Neuropathic symptoms and gait ataxia recover slowly and can persist. Memory impairment from Korsakoff syndrome is often permanent.

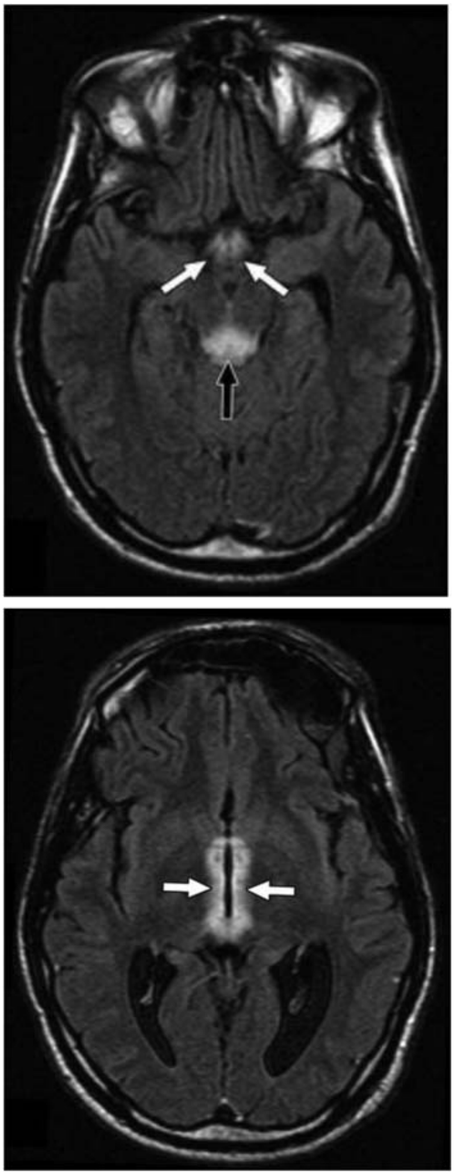

FIGURE 15-2 ■ Axial fluid-attenuated inversion recovery (FLAIR) brain MRI in a patient with Wernicke encephalopathy demonstrating hyperintensity in the periventricular region of the third ventricle, periaqueductal region, and mammillary bodies (*arrows*). (Reprinted with permission from Zuccoli G, Pipitone N. Neuroimaging findings in acute Wernicke's encephalopathy: review of the literature. Am J Roentgenol 192:501, 2009. Copyright ©2009.)

PYRIDOXINE (B_6) DEFICIENCY

Pyridoxine, or vitamin B_6, is a water-soluble vitamin involved in tryptophan, methionine, and gamma aminobutyric acid (GABA) metabolism. The active form of pyridoxine is pyridoxal 5'-phosphate (PLP), a coenzyme that is critical in amino acid and sphingolipid metabolism, as well as the biosynthesis of glucose, many neurotransmitters, and heme.

Etiology

Pyridoxine is abundant in meat, fish, eggs, and dairy products. Pyridoxine must be obtained exogenously and is absorbed in the small intestine. As most adult diets provide adequate pyridoxine, clinical deficiency is predominantly seen as a side effect of pyridoxine-antagonizing medications such as isonicotinic acid hydrazide, hydralazine, and penicillamine. The elderly, pregnant and lactating women, alcoholics, those with sickle cell anemia, and patients with chronic gastrointestinal or malabsorptive conditions are additionally susceptible to pyridoxine deficiency. Genetic mutations can result in an infantile deficiency syndrome.

Clinical Manifestations

Autosomal recessive mutations in the antiquitin gene results in inactivation of PLP and can manifest with pyridoxine-responsive seizures in adequately nourished neonates. Rarely, seizures may develop in breastfeeding infants of malnourished mothers. In adults, chronic pyridoxine deficiency causes a painful sensorimotor peripheral neuropathy. Patients may additionally develop a microcytic hypochromic or sideroblastic anemia. A pellagra-type syndrome with skin, gastrointestinal, and cognitive abnormalities has been described due to abnormal tryptophan metabolism and subsequent niacin deficiency. Conversely, ingestion of pyridoxine exceeding 100 mg per day as seen with excessive vitamin intake can result in a pure sensory neuropathy or dorsal root ganglionopathy.

Diagnosis

Pyridoxine deficiency is often diagnosed clinically and confirmed through measurement of serum PLP levels. An empiric diagnostic trial of pyridoxine is indicated for neonatal seizures. Elevation of pipecolic acid and α-amino adipic semialdehyde levels is seen in infants with genetic pyridoxine-dependent seizures and can be measured in the serum, urine, and cerebrospinal fluid. In adults, serum PLP levels in excess of 20 to 30 nmol/L are considered indicative of adequate pyridoxine status. Elevated serum homocysteine levels following a methionine load can also be seen with pyridoxine deficiency but are rarely measured.

Treatment

Infantile seizures are usually responsive to high doses of pyridoxine but require years of oral maintenance therapy as seizures will recur days after treatment cessation. Drug-induced neuropathy often recovers with discontinuation of the offending agent and oral pyridoxine replacement at 50 to 100 mg/day. One must avoid excess supplementation to prevent associated toxic sensory neuropathy, which additionally is reversible. Treatment of any underlying gastrointestinal, malabsorptive, or hematologic disease is indicated.

NIACIN DEFICIENCY

Etiology

Niacin, or vitamin B_3, is an end-product of tryptophan metabolism involved in carbohydrate metabolism. Niacin deficiency results in the clinical syndrome of pellagra, and is seen primarily in developing countries where corn is the primary carbohydrate source, since corn lacks niacin and tryptophan. Several vitamins and minerals are necessary for the conversion of tryptophan to niacin, including iron, copper, vitamin B_2, and vitamin B_6. Deficiency of vitamin B_6 may result in secondary niacin deficiency. Niacin deficiency may also develop in alcoholics, those with malabsorption, and bacterial overgrowth conditions. Hartnup syndrome may also result in pellagra due to an impairment in conversion of tryptophan to niacin.

Clinical Manifestations

Niacin deficiency affects the skin, gastrointestinal tract, and the nervous system, but skin and gastrointestinal manifestations are frequently absent. Potential gastrointestinal manifestations of pellagra include stomatitis, abdominal pain, and diarrhea. A hyperkeratotic rash, preferentially involving the face, chest, and dorsum of the hands and feet may be seen. Potential neurologic manifestations include encephalopathy, coma, and peripheral neuropathy.

Diagnosis and Treatment

There are currently no reliable serologic studies to identify niacin deficiency. However, measurement of urinary excretion of the methylated niacin metabolites N^1-methylnicotinamide and N^1-methyl-2-pyridone-5-carboxamide can assess niacin status. Oral or parenteral nicotinic acid is administered three times daily.

VITAMIN A DEFICIENCY

Etiology

Vitamin A refers to a collective group of fat-soluble retinoids that includes retinol, retinal, retinoic acid, and retinyl esters. Vitamin A plays an important role in vision, reproduction, and cellular communication. Preformed vitamin A (retinol and retinyl ester) and provitamin A carotenoids are available in the diet. Preformed vitamin A is found in animal sources including dairy products, fish, and meat, while the provitamin A carotenoids (such as beta-carotene) are present in various plant sources. These forms of vitamin A are converted intracellularly into retinal and retinoic acid, the biologically active forms of vitamin A.

The various forms of vitamin A are absorbed primarily in the duodenum and stored in the liver as retinyl esters. Vitamin A deficiency may result from dietary restriction (e.g., diets lacking beta-carotene, alcoholics, the elderly), and may develop in conditions associated with fat malabsorption such as celiac disease, pancreatitis, cystic fibrosis, biliary atresia, and cholecystatic liver disease.

Clinical Manifestations

Chronic, excessive ingestion of vitamin A may lead to headache, increased intracranial pressure, nausea, dizziness, skin changes, bone and joint pain, coma, and even death. Conversely, vitamin A deficiency can cause night blindness, corneal dryness and keratinization, white foamy spots on the cornea (Bitot spots), dysgeusia, skin hyperkeratosis, and hyperkeratosis of the respiratory, gastrointestinal, and urinary tracts.

Diagnosis and Treatment

Assessment of vitamin A levels establishes states of vitamin A deficiency or toxicity. Oral vitamin A supplementation is used to treat vitamin A deficiency.

VITAMIN D DEFICIENCY

Vitamin D is a fat-soluble vitamin that promotes calcium absorption in the gut, thereby maintaining normal serum calcium and phosphate concentrations and enabling normal bone mineralization, bone growth, and remodeling. Vitamin D is also involved in cell growth modulation, neuromuscular function, immune function, and reduction of inflammation. There are two forms of vitamin D: vitamin D_2 or ergocalciferol (produced by plants) and vitamin D_3 or cholecalciferol (produced by sunlight conversion of 7-dehydrocholesterol in the skin).

Etiology

Very few foods in the human diet contain vitamin D. Fatty fish (such as tuna, salmon, mackerel) and fish liver contain the highest amounts, while smaller amounts can be found in beef liver, cheese, and egg yolk. The majority of vitamin D in the American diet comes from fortified foods such as milk, some breakfast cereals, orange juice, and various other foods. However, most people obtain most of their vitamin D needs through sun exposure.

Vitamin D is absorbed passively in the small intestine, then bound to lipoproteins and transported to the liver by chylomicrons. In the liver, vitamin D is hydroxylated to 25-(OH)-vitamin D, and subsequently hydroxylated a second time to 1,25-(OH)-vitamin D in the kidneys. 1,25-(OH)-vitamin D is the biologically active form.

Causes of vitamin D deficiency include inadequate sun exposure, dietary insufficiency, gastrectomy and gastric bypass surgery, pancreatic disease, liver disease, renal disease, and malabsorption. As is true with the other vitamin deficiencies, inflammatory bowel disease, celiac disease, extensive small intestine resection, and cholestatic liver disease may cause vitamin D deficiency. Phenobarbital and phenytoin inhibit vitamin D hydroxylation in the liver. Breastfed infants are at risk because breast milk does not have adequate levels to meet vitamin D requirements. People with dark skin are also at greater risk for developing vitamin D deficiency because melanin in the epidermis reduces the skin's ability to generate cholecalciferol. Other risk factors include older age, sunscreen use, high latitudes, and other environmental factors such as pollution, extent of cloud cover, and ozone levels.

Clinical Manifestations

Vitamin D deficiency may cause rickets in children and osteomalacia in adults due to defective bone mineralization. A proximal myopathy may develop, often associated with bone pain and osteomalacia. A multitude of other medical conditions have been associated with suboptimal vitamin D levels including hypertension, diabetes mellitus, certain types of cancers, and multiple sclerosis, but more definitive, prospective studies are necessary to establish definite risk. The role of vitamin D deficiency in multiple sclerosis risk has not been conclusively established to date. Multiple sclerosis incidence and prevalence are increased at higher latitudes, but the roles of sun exposure and vitamin D deficiency may both be factors in increased risk. Treatment with vitamin D in multiple sclerosis has not been demonstrated to be of benefit in reducing risk of relapse, brain MRI lesions, or decreasing disability.[10]

Diagnosis and Treatment

Total 25-(OH)-vitamin D is the best laboratory study to assess vitamin D body stores, and can be used to diagnose and monitor vitamin D deficiency. A frequently employed strategy to treat severe vitamin D deficiency is to give a loading dose of 50,000 IU of vitamin D once weekly for 2 to 3 months or three times weekly for 1 month. A lower dose may be utilized in mild to moderate vitamin D deficiency; a daily dose of 800 to 2,000 IU is necessary.

LATHYRISM

Lathyrism is one of the oldest known neurotoxic disorders and results from excessive consumption of *Lathyrus sativus*, a species of chickpea. Lathyrism is currently restricted to areas in Bangladesh, India, and Ethiopia, resulting in nonprogressive, but irreversible, spastic paraparesis. Neurophysiologic studies suggest anterior horn cell impairment, and neuropathologic studies have demonstrated myelin loss in pyramidal pathways and anterior horn cell involvement. It has been suggested that lathyrism results from the toxin beta-*N*-oxalyl-amino-L-alanine, an agonist of the excitatory neurotransmitter glutamate.[11]

KONZO

Konzo is a neurologic disorder confined to rural Africa, resulting from a diet of excessive cyanogen consumption from inadequately processed cassava root combined with a low-protein diet. Cassava root is drought tolerant and therefore may become the major or sole food source during agricultural crises. Konzo is characterized clinically by a symmetric, nonprogressive spastic paraparesis.

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SECTION

3

Renal and Electrolyte Disorders

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CHAPTER

16

Neurologic Dysfunction and Kidney Disease

MICHAEL J. AMINOFF

UREMIC ENCEPHALOPATHY
- Pathophysiology
- Clinical Features
- Investigations
- Treatment of Uremic Convulsions

UREMIC NEUROPATHY
- Polyneuropathy
  - *Pathophysiology*
  - *Clinical Features*
  - *Treatment*
- Autonomic Neuropathy

RESTLESS LEGS SYNDROME

OTHER MOVEMENT DISORDERS

UREMIC MYOPATHY

STROKE

OPTIC NEUROPATHY

NEUROLOGIC COMPLICATIONS OF NEPHROTIC SYNDROME

NEUROLOGIC COMPLICATIONS OF DIALYSIS
- Entrapment Mononeuropathies
  - *Carpal Tunnel Syndrome*
  - *Ulnar Nerve Lesions*
- Ischemic Neuropathy
- Dialysis Dysequilibrium Syndrome
- Wernicke Encephalopathy
- Dialysis Dementia
  - *Clinical Aspects*
  - *Pathogenesis*
  - *Treatment*

COMPLICATIONS OF TRANSPLANTATION
- Femoral and Related Neuropathy
- Development of Malignant Disease
- Brain Tumors
- Central Nervous System Infections

HEREDITARY DISORDERS OF THE NERVOUS SYSTEM AND KIDNEYS
- Fabry Disease
- von Hippel—Lindau Disease
- Polycystic Kidney Disease
- Other Hereditary Disorders

The neurologic aspects of renal disease and the neurologic complications of dialysis and renal transplantation are discussed in this chapter. The neurologic complications of renal carcinoma are not considered, but paraneoplastic complications of malignancy are considered in Chapter 27, and the neurologic consequences of radiation and chemotherapy in Chapter 28. The subject itself is complicated because many of the causes of renal failure lead to neurologic complications that also occur in uremia. Thus, collagen vascular diseases are commonly associated with encephalopathy or seizures, and diabetes with neuropathy or encephalopathy. Attention here is directed primarily to complications that are a direct consequence of the renal failure and its treatment rather than to the underlying cause of the kidney disease. In addition, however, certain hereditary disorders that affect both the nervous system and the kidneys are considered. In order to limit the size of the chapter, the bibliography has been restricted, but a more detailed list of references can be found in previous editions of this book.

UREMIC ENCEPHALOPATHY

The neurologic consequences of uremia resemble other metabolic and toxic disorders of the central nervous system (CNS). Thus, the clinical features of the encephalopathy that occurs in uremic patients include an impairment of external awareness that ranges from a mild confusional state, with diminished attention and concentration, to coma. The

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presence of coma may indicate severe uremia or reflect a complication such as hypertensive encephalopathy, posterior reversible encephalopathy syndrome (PRES, discussed later), fluid and electrolyte disturbances, seizures, or sepsis. Other causes of an encephalopathy in uremic patients include dialysis, thiamine deficiency, drug toxicity, and transplant rejection. Finally, the encephalopathy and renal impairment may both relate independently to the same underlying systemic illness, such as diabetes or connective tissue diseases. All these factors complicate clinical assessment.

In addition to an alteration in external awareness, patients with uremic encephalopathy may have cognitive changes (impaired memory and executive functions), seizures, dysarthria, gait ataxia, asterixis, tremor, and multifocal myoclonus. As with all metabolic encephalopathies, symptoms and signs typically fluctuate in severity over short periods of time, such as over the course of a day or from day to day.

Pathophysiology

Uremic encephalopathy relates to a variety of metabolic abnormalities, with the accumulation of numerous metabolites, acid–base disturbances, imbalance in excitatory and inhibitory neurotransmitters, inflammatory changes, and hormonal disturbances leading to cerebral dysfunction. The European Uremic Toxin Work Group has listed 90 compounds considered to be uremic toxins; 68 have a molecular weight less than 500 Da, 12 exceed 12,000 Da, and 10 have a molecular weight between 500 and 12,000 Da.[1] A few merit brief discussion here. Retention of urea occurs; urea clearance, even in well-dialyzed patients, amounts to only one-sixth of physiologic clearance.[1] Accumulation of guanidinosuccinic acid, methylguanidine, guanidine, and creatinine, all of which are guanidine compounds, in the serum and cerebrospinal fluid (CSF) of uremic patients, may relate to uremic seizures and cognitive dysfunction. Oxidative stress, homocysteinemia, activation of *N*-methyl-D-aspartate (NMDA) receptors, and inhibition of γ-aminobutyric acid-A ($GABA_A$) transmission may be involved. It remains unclear whether low-level aluminum overload in renal failure causes gradual deterioration in cerebral function. Abnormalities of the membrane pumps for both Na^+,K^+-adenosine triphosphatase and calcium ions may be of clinical relevance, and cerebrovascular factors may be contributory.

Hormonal changes may also be important. Serum concentrations of parathyroid hormone, growth hormone, prolactin, luteinizing hormone, insulin, and glucagon are elevated in uremic patients. Parathyroid hormone levels increase with the severity of the encephalopathy, and alterations in brain calcium could influence neurotransmitter release, the sodium–potassium pump, intracellular enzyme activity, and intracellular metabolic processes, and thereby may affect cerebral function. The calcium content of the cerebral cortex is greatly increased in uremia, and this is unrelated to alterations in calcium concentration in the plasma or CSF. Both clinical and electroencephalographic (EEG) abnormalities and changes in cerebral calcium concentration are improved by parathyroidectomy.

Clinical Features

The clinical features of uremic encephalopathy do not show a good correlation with any single laboratory abnormality but can sometimes be related to the rate at which renal failure develops. Thus, stupor and coma are relatively common in acute renal failure, whereas symptoms may be less conspicuous and progression more insidious despite more marked laboratory abnormalities in chronic renal failure. Dialysis relieves or prevents some of the more severe features of this encephalopathy, but in contrast to the continuous function of normal kidneys, the removal of uremic toxins in dialysis is achieved by a one-step, membrane-based process and is intermittent.

The most reliable early indicators of uremic encephalopathy are a waxing and waning reduction in alertness and impaired external awareness. The ability to concentrate is impaired, so that patients seem preoccupied and apathetic, with a poor attention span; they become increasingly disoriented with regard to place and time and may exhibit emotional lability and sleep inversion. An impairment of higher cognitive abilities, such as of executive function, becomes evident, and patients become increasingly forgetful and apathetic. With progression, patients become more obtunded so that it may then be necessary to shout or gently shake them to engage their attention and elicit any responses, which are likely to be of variable accuracy and relevance. Delusions, illusions, and hallucinations (typically visual) often develop, and patients may become agitated and excited, with an acute delirium that eventually is replaced by stupor and a preterminal coma.

Tremulousness may be conspicuous and usually occurs before asterixis is found. A coarse postural tremor is seen in the fingers of the outstretched hands, and a kinetic tremor is also common. Asterixis is a nonspecific sign of metabolic cerebral dysfunction. An intermittent loss of postural tone produces the so-called flapping tremor of asterixis after several seconds when the upper limbs are held outstretched with the elbows and wrists hyperextended and fingers spread apart; irregular flexion–extension occurs at the wrist and of the fingers at the metacarpophalangeal joints, with flexion being the more rapid phase. There is complete electrical silence in the wrist flexors and extensors during the downward (flexor) movements, followed by electrical activity in the extensors as they restore the limb's posture. The axial structures, including the trunk or neck, may also be affected. Asterixis can also be demonstrated in the lower limbs, and flapping may even be elicited in the face by forceful eyelid closure, strong retraction of the corners of the mouth, pursing of the lips, or protrusion of the tongue, provided that some degree of voluntary muscle control persists. In obtunded or comatose patients, or others in whom voluntary effort is limited, asterixis can still be elicited, but at the hip joints. With the patient lying supine, the examiner grasps both ankles of the supine patient and moves the feet upward toward the patient's body, flexing and abducting the thighs: irregular abduction–adduction movements at the hips indicate asterixis.

Spontaneous and stimulus-sensitive myoclonus is common in uremia and in other metabolic encephalopathies and reflects increased cerebral excitability. The myoclonus is typically multifocal, irregular, and asymmetric; it may be precipitated by voluntary movement (action myoclonus). The myoclonic jerks may be especially conspicuous in the facial and proximal limb muscles. Uremic myoclonus in humans resembles the reticular reflex form of postanoxic action myoclonus. It is usually not associated with EEG spike discharges, although such discharges have sometimes been encountered with the myoclonus. The myoclonus may respond to clonazepam. Multifocal myoclonus is sometimes so intense that muscles appear to be fasciculating (*uremic twitching*). Tetany may occur.

Seizures are common. They are usually generalized convulsions, may be multiple, and are often multifactorial in etiology. In acute renal failure, convulsions commonly occur several days after onset, during the anuric or oliguric phase. In chronic renal failure, they tend to occur with advanced disease, often developing preterminally; they may relate to the uremia itself or to electrolyte disturbances, medications (such as penicillin, aminophylline, or isoniazid), or an associated *posterior reversible encephalopathy syndrome* (characterized by vasogenic white-matter edema predominantly localized to the posterior cerebral hemispheres on imaging studies, as shown in Fig. 16-1). Their incidence has declined, perhaps because of more effective treatment of renal failure and its complications. Seizures also occur in patients undergoing hemodialysis as part of the *dialysis dysequilibrium syndrome* (discussed later). Focal seizures sometimes occur. Occasionally patients develop nonconvulsive status epilepticus that may not be recognized unless an EEG is obtained.

During the early stages of uremia, patients may be clumsy or have an unsteady gait. Paratonia (*gegenhalten*), a variable, velocity-dependent resistance to passive movement, especially rapid movement, is common, and grasp and palmomental reflexes may be present, presumably as a result of a depression of frontal lobe function. As uremia advances, extensor muscle tone increases and may be asymmetric; opisthotonos or decorticate posturing of the limbs may eventually occur. Motor deficits may include transient or alternating hemiparesis that shifts sides during the course of the illness, flaccid quadriparesis related to hyperkalemia, or distal weakness from uremic neuropathy. The tendon reflexes are generally brisk unless a significant peripheral neuropathy is present and they may be asymmetric; Babinski signs are often present.

Encephalopathy may occur in uremic patients for reasons other than uremia, such as in relation to dialysis, thiamine deficiency, electrolyte imbalance, medication-related toxicity, and graft rejection. These disorders are considered in later sections of this chapter.

Investigations

Laboratory studies provide evidence of impaired renal function but are of limited utility in monitoring the course of the encephalopathy. Furthermore, abnormal renal function tests do not exclude other causes of encephalopathy. An underlying structural lesion must be excluded in uremic patients who have

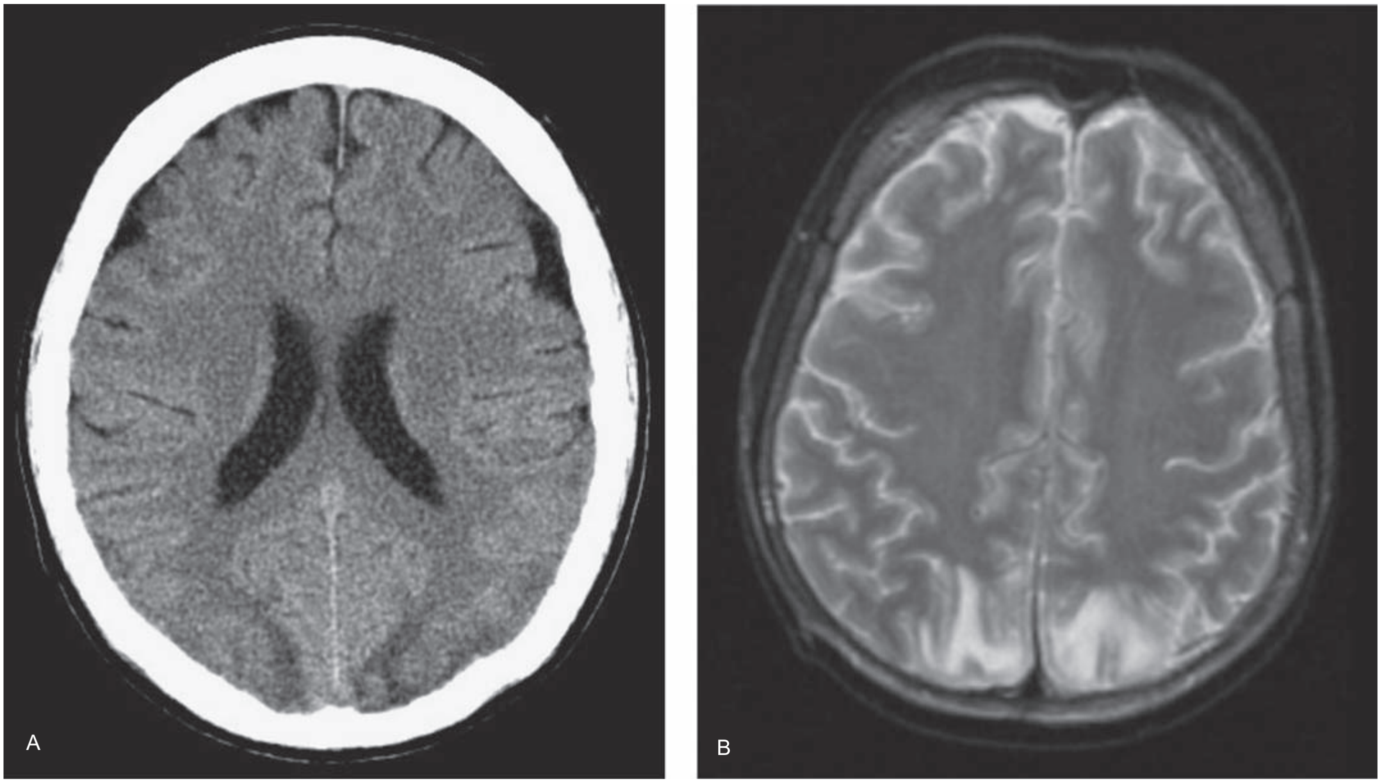

FIGURE 16-1 ■ Imaging findings of a patient with seizures who was diagnosed with posterior reversible encephalopathy syndrome. *A*, Axial computed tomography (CT) scan demonstrates bilateral low-density involvement of the occipital lobes. *B*, Axial T2-weighted magnetic resonance imaging (MRI) shows high signal intensity lesions without mass effect involving white matter bilaterally in the occipital lobes. (Courtesy of William P. Dillon, MD, University of California, San Francisco.)

had seizures, especially when focal or multiple seizures have occurred.

The CSF is commonly abnormal, with a pleocytosis that is unrelated to the degree of azotemia and an increased protein content that sometimes exceeds 100 mg/dL. The findings may thus suggest a mild aseptic meningitis.

The EEG is diffusely slowed, with an excess of intermittent or continuous theta and delta waves that may show a frontal emphasis, perhaps reflecting a decreased cerebral metabolic rate. Triphasic waves are often present, with an anterior predominance (Fig. 16-2). Bilateral spike–wave complexes may be present either in the resting EEG or with photic stimulation. The EEG becomes increasingly slowed with progression of the encephalopathy, so that delta activity becomes more continuous; the findings correlate best with the level of retained nitrogenous compounds, although no clear relationship exists between the EEG and a specific laboratory abnormality. Similarly, there are delays of visual, auditory, and somatosensory evoked cerebral potentials. Event-related potentials reveal abnormalities even in asymptomatic patients, with an increase in P3 latency. In a study involving transcranial magnetic stimulation, 36 patients with end-stage renal disease were evaluated at different stages of the disease and under different treatment.[2] Patients on conservative treatment showed a significant reduction of short-interval intracortical inhibition that could be reversed by hemodialysis, peritoneal dialysis, or renal transplantation. After hemodialysis, intracortical facilitation increased, and this was inversely correlated with the decline in plasma osmolarity induced by the dialytic procedure. In other words, patients showed alterations in cortical excitability that were reversed by treatment of the renal disease.

Cerebral imaging studies are of limited help except in excluding other, structural causes of the encephalopathy. They may reveal a reversible, predominantly posterior leukoencephalopathy, with subcortical edema without infarction. There may be multiple areas of

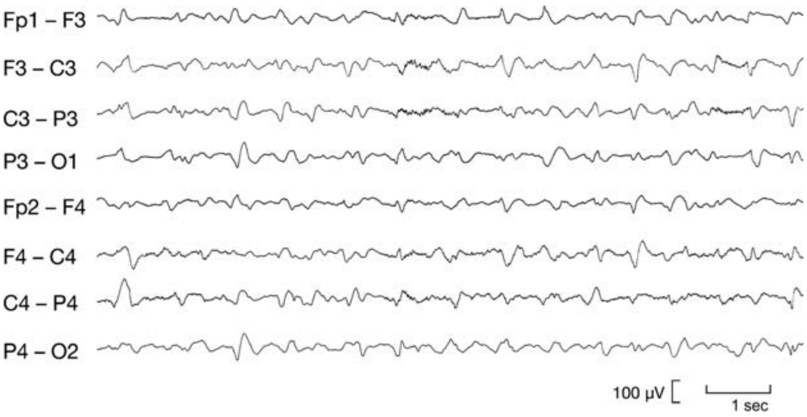

FIGURE 16-2 ■ Electroencephalogram (EEG) showing a diffusely slowed background with triphasic waves in a patient with uremic encephalopathy.

symmetric edema in the basal ganglia, brainstem, or cerebellum, with—in severe cases—focal infarcts, sometimes hemorrhagic.

Treatment of Uremic Convulsions

Treatment involves correction of renal failure and related metabolic abnormalities. In patients who have had seizures, anticonvulsant medication may be required, especially when the convulsions are of uncertain cause. If status epilepticus occurs, it is managed as in other circumstances.

Various considerations make anticonvulsant therapy difficult to manage in uremia. As discussed in Chapter 57, plasma protein binding and renal excretion are reduced, and dialysis may remove drugs from the circulation. Phenytoin was often used in the past in this context; reduced protein binding leads to a greater volume of distribution and lower serum concentrations, but the proportion of unbound (active) phenytoin increases and maintains the benefit of a given dose. Free phenytoin rather than total plasma levels are used to monitor treatment; the optimal therapeutic range is 1 to 2 μg/mL. The total daily dose generally need not be changed, but it is probably best taken divided rather than in a single dose. Dialysis does not remove phenytoin from the circulation to any significant extent. Plasma phenobarbital levels are unaffected by renal insufficiency. Lower doses of phenobarbital are used for long-term maintenance therapy, however, because the drug may accumulate; additional doses may be required after dialysis. Primidone and its metabolites may also accumulate, causing toxicity in uremic patients.

Valproic acid is helpful for treating myoclonic seizures and generalized convulsions in uremic patients. Protein binding decreases, but the free fraction remains constant. Dialysis does not necessitate additional doses.

Serum carbamazepine levels are unchanged, and dosing does not need alteration. Impaired renal function leads to decreased clearance of felbamate, gabapentin, topiramate, levetiracetam, vigabatrin, pregabalin, and oxcarbazepine. Gabapentin, pregabalin, and topiramate are excreted mainly by the kidneys, and the daily dose will need to be reduced in uremic patients; dosing of zonisamide may also need reduction. Hemodialysis necessitates additional doses of levetiracetam (typically 250 to 500 mg) and gabapentin (200 to 300 mg); supplemental doses of topiramate and pregabalin after hemodialysis may also be required. Extra doses of zonisamide may not be necessary if this drug is given in a single daily dose after dialysis sessions. Tiagabine and lamotrigine pharmacokinetics show little change even in severe uremia, and dosage adjustment is usually unnecessary.

UREMIC NEUROPATHY

Polyneuropathy

Peripheral nerve function becomes impaired at glomerular filtration rates of less than 12 mL/min, with clinical deficits developing at rates of about 6 mL/min. More than 50 percent of patients with end-stage renal disease have clinical (neuropathic symptoms or signs) or electrophysiologic abnormalities, the exact number depending on the series and diagnostic criteria utilized.

PATHOPHYSIOLOGY

Because uremic neuropathy improves with dialysis, uremic neuropathy has been attributed to the accumulation of dialyzable metabolites. Hemodialysis regimens sufficient to control urea or creatinine may nevertheless fail to prevent the development of neuropathy, and this observation led to the "middle molecule" hypothesis. In particular, the lower prevalence of neuropathy in patients on peritoneal dialysis than on hemodialysis suggested that the responsible substance was better dialyzed by the peritoneum, and it was proposed that these substances might be in the middle-molecule range (500 to 12,000 Da), which is poorly cleared by hemodialysis membranes. The adoption of dialysis strategies to improve the clearance of middle molecules reduced the rates of severe neuropathy, but the identity of the responsible neurotoxins has remained elusive.

Secondary hyperparathyroidism complicates chronic renal failure and some evidence exists for the neurotoxicity of parathyroid hormone, as discussed earlier. Studies in uremic patients of the effect of parathyroid hormone on peripheral nerves, however, have yielded both supporting and conflicting results.

It has been proposed that mild hyperkalemia has a role in the genesis of the neuropathy. Hyperkalemia typically recurs within a few hours of a dialysis session as a result of re-equilibration between intracellular and extracellular fluid compartments. Prolonged hyperkalemia may disrupt normal ionic gradients and activate Ca^{++}-mediated processes that are damaging to axons. Motor and sensory nerve excitability has been studied in relation to changes in serum levels of potential neurotoxins, including calcium and potassium ions, urea, uric acid, and certain middle molecules. Predialysis measures of nerve excitability were abnormal, consistent with axonal depolarization, and correlated strongly with serum potassium levels, suggesting that hyperkalemic depolarization did underlie the development of uremic neuropathy.[3] The severity of symptoms also correlated with excitability abnormalities. Most nerve excitability parameters were normalized by hemodialysis. The findings thus supported the belief that hyperkalemia contributes to the development of neuropathy. There was no evidence of significant Na^+/K^+ pump dysfunction.

If hyperkalemia does indeed have a role in mediating these abnormalities, measures of dialysis adequacy based solely on blood urea or creatinine concentrations may be inadequate for determining whether dialysis will prevent neurotoxicity. Monitoring the serum potassium level to ensure that it is maintained within normal limits between periods of dialysis may be more relevant in this regard. Preliminary evidence suggests that dietary potassium restriction confers some degree of neuroprotection in chronic kidney disease.[3]

CLINICAL FEATURES

Uremic neuropathy is more common in men than women and in adults than children. It is characterized by a length-dependent, symmetric, mixed sensorimotor polyneuropathy of axonal type that resembles other axonal metabolic-toxic neuropathies. Its clinical manifestations, severity, and rate of progression are variable. As with uremic encephalopathy, its severity correlates poorly with biochemical abnormalities in the blood, but neuropathy is more likely to develop in chronic or severe renal failure.

Initial symptoms commonly consist of dysesthesias distally in the legs; muscle cramps may also be troublesome. The restless legs syndrome often develops before or with the clinical onset of neuropathy, and its occurrence may therefore indicate incipient peripheral nerve involvement. As with many other neuropathies, the earliest clinical signs are of impaired vibration appreciation and depressed or absent tendon reflexes distally in the legs, indicating involvement of large-diameter myelinated fibers. Autonomic involvement may occur but is usually mild.

Progression is typically insidious over many months but occasionally is rapid, leading early to severe disability, sometimes painful. A more progressive, predominantly motor subacute neuropathy may occur in uremic patients with diabetes and lead to severe weakness over a few weeks or months; nerve conduction studies typically demonstrate features of an axonal neuropathy but may show demyelination features, and the neuropathy may respond to transplantation or to a switch from conventional to high-flux hemodialysis. The course may be arrested at any time despite continuing or worsening renal failure.

It is hard to predict the likely clinical course in individual patients. Most patients are left with distal motor and sensory deficits, but some become severely disabled with a flaccid quadriparesis or paraparesis. Severe neuropathy has become less prevalent with the introduction of dialysis and transplantation techniques but remains common.

Histopathologic examination of nerve biopsy specimens confirms that the neuropathy is a length-dependent axonal degeneration accompanied by secondary demyelination, although in some cases the demyelination seems the predominant finding; damaged endoneural blood capillaries may also be found and support an ischemic theory as one mechanism in the pathogenesis of uremic neuropathy.

Nerve conduction studies also support an axonal process, with reduced conduction velocities and response amplitudes; abnormalities are common even in clinically unaffected nerves. The amplitude of the sensory nerve action potential is affected particularly, especially that of the sural nerve. Large fibers are affected more often than small fibers, but in occasional patients a predominantly small-fiber neuropathy occurs. The findings on nerve conduction studies may improve after effective treatment of the underlying renal failure, sometimes very rapidly, but this is not always the case; sensory nerve conduction velocities in the median, ulnar, and sural nerves may be the most sensitive electrophysiologic indices of the beneficial effect of hemodialysis. Needle electromyography may reveal evidence of denervation, particularly in the distal muscles of the legs. Abnormalities of late responses (F waves and H reflexes) are frequent and may be helpful early in the course of renal failure, when standard nerve conduction study results are sometimes normal.

Laaksonen and colleagues examined the clinical severity of uremic neuropathy in 21 patients, using a modified version of the neuropathy symptom score combined with results of electrophysiologic studies.[4] They found that 81 percent of uremic patients were diagnosed with neuropathy: the neuropathy was asymptomatic in 19 percent, associated with nondisabling symptoms in 48 percent, and accompanied by disabling symptoms in 14 percent.

TREATMENT

Uremic polyneuropathy may stabilize or even show some improvement with dialysis, but mild progression is not uncommon and recovery from severe neuropathy is unlikely. Renal transplantation improves uremic neuropathy, sometimes very rapidly and with a negative correlation between electrophysiologic change and serum creatinine and *myo*-inositol concentrations, suggesting that metabolic factors may underlie the rapid improvement. In other instances, improvement is more gradual over a number of months, is characterized electrophysiologically by improvement in motor and sensory conduction velocities, and is often incomplete, perhaps because the main reason for improvement is segmental remyelination, with some fibers remaining degenerate in severe neuropathies.

Autonomic Neuropathy

Uremic patients may develop postural hypotension, impaired sweating, impotence, gastrointestinal disturbances, and other dysautonomic symptoms, which progress in some patients—but not all—despite continuing hemodialysis.[5] The dysautonomia correlates with the presence or severity of peripheral neuropathy in some but not all patients and may be corrected by renal transplantation. The mechanism underlying the development of uremic autonomic neuropathy is unknown. In patients with diabetic renal failure, dysautonomia may relate also to the diabetes. Studies of both cardiovagal and sympathetic function (discussed in Chapter 8) have revealed objective evidence of dysautonomia that may be subclinical.

Intradialytic hypotension is a frequent complication of hemodialysis and has been shown to relate in many cases to impaired autonomic function regardless of whether a peripheral neuropathy is present. Midodrine may have a role in the therapy of patients with intradialytic hypotension.

Dialysis may not benefit autonomic neuropathy. After renal transplantation, autonomic function may improve or normalize but at a variable rate and typically slower and less completely than large-fiber neuropathies. Specific symptomatic treatments, for example, with phosphodiesterase inhibitors such as sildenafil for erectile dysfunction, may be helpful.

RESTLESS LEGS SYNDROME

Development of the restless legs syndrome may indicate incipient peripheral nerve involvement or may occur as an isolated disorder. Patients develop an irresistible urge to move the legs that is worse at night and during periods of inactivity. They complain of curious sensations—often described as creeping, crawling, prickling, or itchy feelings—in the lower limbs, and these tend to be worse in the evening or when the limbs are not in motion. Such sensations are experienced most commonly in the legs but occasionally occur in the thighs or feet; the upper limbs are also sometimes involved. The disorder may occur in nondialyzed patients with chronic renal failure. When it occurs in uremic patients undergoing hemodialysis, it has been related to low hemoglobin levels, high serum phosphorus levels, and high anxiety levels. Treatment of restless legs syndrome is with clonazepam, dopamine agonists, levodopa, certain anticonvulsants, or opioids (propoxyphene or codeine) taken at bedtime, but the response often declines with time. Co-existing anemia and hyperphosphatemia should be corrected. Successful renal transplantation may ameliorate or eliminate symptoms within a few weeks, but symptoms can recur with transplant rejection and the disorder remains more common than in the general population.

OTHER MOVEMENT DISORDERS

A variety of movement disorders in addition to restless legs syndrome are seen in patients with kidney disease. Tremor, spontaneous and stimulus-sensitive multifocal myoclonus, and asterixis are all features of uremic encephalopathy, and imaging studies often reveal edema in the basal ganglia as well as more widely, and sometimes frank infarcts or hemorrhage. The myoclonus, discussed earlier, may respond to clonazepam. Parkinsonism and dystonia may also occur, often as a complication of subcortical strokes, and are discussed in Chapter 58.

UREMIC MYOPATHY

Proximal muscle weakness, atrophy, and muscle fatigue are common in uremic patients, and the progression of the underlying myopathy parallels the decline in renal function. Muscle involvement is more common in patients undergoing chronic hemodialysis. Onset is insidious. The hip girdle is affected more than the shoulder girdle. The primary systemic disease responsible for the renal failure—or its treatment, such as with corticosteroids—may lead to a myopathy. Other causal factors include malnutrition, anemia, accumulation of toxins (including aluminum and iron), endocrine disorders (such as secondary hyperparathyroidism), hypercalcemia, hypophosphatemia, vitamin D deficiency, carnitine deficiency, hyper- and hypokalemia, and physical inactivity. Calciphylaxis in end-stage kidney disease is a rare cause of painful ischemic myopathy; vascular calcification and occlusion of small and medium-sized arteries is responsible. Dialysis-associated systemic fibrosis may cause a myopathy. Myopathy may relate to β_2-microglobulin-associated amyloidosis.

Treatment is of the underlying cause of the muscle weakness. Hemodialysis patients treated with vitamin D have been found to have greater muscle size and power than those not receiving vitamin supplementation. Adequate protein intake should be assured and anemia corrected. Physical therapy helps to improve muscle strength. Renal transplantation is sometimes indicated.

STROKE

Chronic kidney disease is common in stroke patients, but the basis of any association between the two is not completely clear. The association could be causal but it could also reflect that stroke and renal disease share cardiovascular risk factors, such as age, diabetes, hypertension, and dyslipidemia.[6] Regardless, meta-analysis of previously published articles suggests that a reduced glomerular filtration rate is a significant risk factor for both ischemic and hemorrhagic stroke, independent of known cardiovascular risk factors. Factors that might be involved include increased inflammatory mediators, oxidative stress, thrombogenic factors, hyperhomocysteinemia, and reduced klotho protein (which is expressed predominantly in the distal renal tubule and thus declines with advancing kidney disease).[6]

Patients with renal disease commonly have a greater volume of white matter lesions on MRI and more silent brain infarcts than otherwise. As the kidney disease advances, the prevalence of these silent infarcts increases. Thus, there seems to be a significant relationship between impaired kidney function and small-vessel disease, which is itself associated with cerebral microbleeds independent of age, sex, and blood pressure. There is also evidence that chronic kidney disease affects the presence and severity of carotid atherosclerosis.

Patients with chronic kidney disease (i.e., reduced glomerular filtration rate) generally have poorer outcomes from ischemic strokes than those without kidney involvement. They are more likely to deteriorate while in hospital, and have a greater risk of recurrent stroke or death in hospital. Proteinuria independently contributes to the increased risks of neurologic deterioration, mortality, and poor functional outcome after acute stroke. Proteinuria is also associated with the hemorrhagic transformation of cerebral infarcts. Among patients with hemorrhagic stroke, impaired kidney function is associated with larger hematoma volume, greater mortality or disability, and reduced likelihood of discharge home.

Stroke management is affected by impaired kidney function. Although alteplase (tissue-type plasminogen activator) is metabolized by the liver, patients with chronic kidney disease have worse outcomes and a higher risk of bleeding complications after intravenous thrombolysis than those with normal kidney function. The management of atrial fibrillation poses additional problems. Patients with end-stage renal disease have an increased risk of bleeding and this risk is increased with warfarin. Accordingly, the routine use of warfarin for atrial fibrillation in this context is often limited to those at high risk of stroke, when the aim is to achieve a target international normalized ratio of 2 to 3. The risks with newer anticoagulants are less clear, but apixaban can be used in place of warfarin.

The control of chronic hypertension is particularly important in reducing stroke risk in patients with chronic kidney disease. Antihypertensive treatment should be rigorous, initially with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker to improve renal outcome. In patients with previous atherosclerotic strokes, antiplatelet agents help to reduce secondary stroke risk. Optimizing diabetic control, cessation of smoking, dietary salt restriction, weight reduction, and correction of co-existing anemia may be important in reducing cardiovascular and stroke risk in individual cases, and carotid endarterectomy is worthwhile in selected patients. The risk of stroke is also high in patients receiving chronic hemodialysis, as is discussed in a later section.

OPTIC NEUROPATHY

A progressive unilateral or bilateral optic neuropathy may occur over several days, sometimes as the initial manifestation of end-stage kidney disease; visual loss is accompanied by reduced pupillary response to light and by papillitis. Prompt hemodialysis and corticosteroid therapy may restore vision in some patients. The optic neuropathy may be neurotoxic, ischemic, related to side effects of medication or intracranial hypertension, or inflammatory in nature.

In ischemic optic neuropathy occurring in patients on hemodialysis, co-existing hypotension and anemia are important risk factors, and treatment may require intravenous saline or blood transfusions in addition to the other measures mentioned earlier. Calcific uremic arteriolopathy may also have an etiologic role. Several cases of nonarteritic ischemic optic neuropathy related to hemodialysis have been reported. The optic neuropathy is produced by compromise of oxygen delivery to the optic nerve, resulting in hypoxic swelling, nerve compression in the optic canal, and ischemia of the optic nerve head. Presentation is with sudden, unilateral, painless inferior visual field defect and a fixed unreactive pupil after relative hypotension. This complication must be considered when examining dialysis options, particularly in patients with other risk factors such as hypotension, anemia, and a past history of anterior ischemic optic neuropathy.

NEUROLOGIC COMPLICATIONS OF NEPHROTIC SYNDROME

The nephrotic syndrome, which results from glomerular damage, is characterized by excessive proteinuria in the absence of hematuria, and is accompanied by edema, hypoalbuminemia, and hyperlipidemia. There is an increased risk of arterial or venous thromboembolism, and this may involve the cerebral circulation. The causes of the responsible hypercoagulable state are not entirely clear, but alterations occur in various blood coagulation factors, platelet reactivity, and blood viscosity, and in the fibrinolytic system. Cerebral venous thrombosis—particularly involving the major intracranial venous sinuses—is a well-known complication in patients of any age, signaled by the development of headache, seizures, or clinical features of increased intracranial pressure. Arterial thrombosis is less common but may involve a variety of peripheral arteries, including the carotid artery, sometimes as the initial manifestation of the nephrotic syndrome. Presentation is with transient cerebral ischemic attacks or ischemic stroke. By analogy to patients without nephrotic syndrome, treatment of arterial or venous disease involves anticoagulation, typically with heparin followed by oral anticoagulation.

Posterior reversible encephalopathy syndrome (PRES) has also been associated with the nephrotic syndrome or its treatment with immunosuppressive drugs in children and adults. The disorder is characterized by impaired consciousness, seizures, headache, and transient visual disturbances in the setting of hypertension, and is associated with cortical and subcortical edema manifest by high signal intensity on T2-weighted MRI, especially posteriorly. Fluid-attenuated inversion recovery (FLAIR) imaging improves diagnostic confidence and the conspicuousness of the T2 hyperintensities. The prognosis is usually benign, with symptoms settling after several days of adequate treatment. Treatment involves the control of associated hypertension, the management of seizures, and the withdrawal of any medication that is likely to have been responsible for the disorder.

Certain neuromuscular disorders may relate to the nephrotic syndrome. There have been several case reports of the simultaneous development of nephrotic syndrome and Guillain–Barré syndrome. In one such case, plasmapheresis and corticosteroids led to simultaneous recovery of both disorders, suggesting a common pathogenesis of the two conditions. Myasthenia gravis may co-exist with nephrotic syndrome, and its temporary improvement may result from antibody elimination during proteinuria in nephrotic syndrome.

Pierson syndrome, a rare autosomal recessive disorder due to mutations in the *LAMB2* gene, is characterized by congenital nephrotic syndrome leading to end-stage renal disease, and by microcoria and other ocular abnormalities. Severe hypotonia and psychomotor retardation occur in those surviving infancy.

NEUROLOGIC COMPLICATIONS OF DIALYSIS

Dialysis has been associated with subtle *cognitive alterations*, possibly reflecting an early manifestation of dialysis dementia at a reversible stage. More commonly, psychologic studies have shown significant improvement in short-term memory both after onset of maintenance dialysis and when comparisons are made between the day before and after an individual dialysis treatment session; attentional functions also seem to improve after dialysis. *Subdural hematoma* (Fig. 16-3) may occur in patients on maintenance hemodialysis; it has a 20-times higher incidence than in the general population and is associated with high mortality. The symptoms of the subdural hematoma may be attributed erroneously to dysequilibrium syndrome or dialysis dementia. Its occurrence may relate to anticoagulation used to maintain the patency of the conduit for hemodialysis; platelet function may be impaired in uremia but, in itself, is unlikely to be responsible. A rare case of manganese-induced *parkinsonism* has been described in a patient on maintenance hemodialysis and was attributed to long-term ingestion of a health supplement; the clinical, laboratory, and MRI findings were abnormal, but the patient improved on edetic acid infusion therapy.[7] The occurrence of hemodialysis-related *optic neuropathy* was mentioned in an earlier section. These complications will receive no further discussion here.

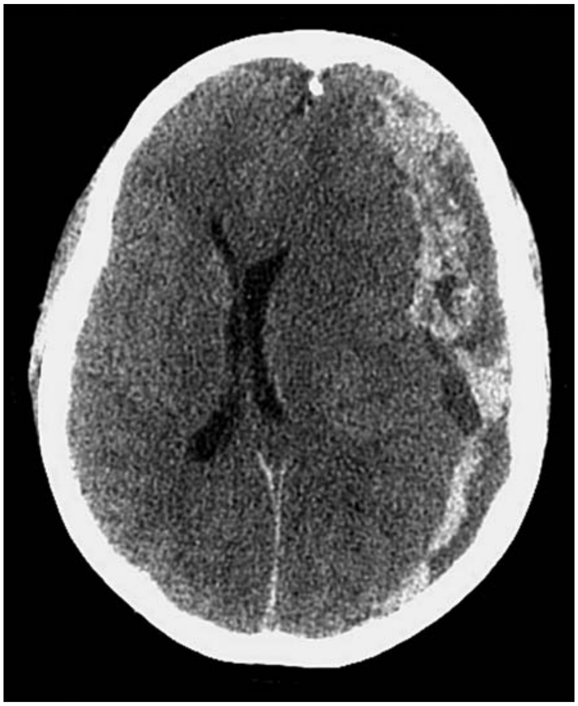

FIGURE 16-3 ■ Axial noncontrast CT scan shows a mixed-density left subdural hematoma producing marked mass effect on the left hemisphere and midline shift. The low density within the subdural hematoma is a feature of active hemorrhage. (Courtesy of William P. Dillon, MD, University of California, San Francisco.)

Muscle *cramps* are common, tending to occur toward the end of a dialysis session: their etiology is uncertain, but plasma volume contraction and hyponatremia are among the factors that have been incriminated. Headache, nausea, and vomiting may also occur during dialysis, sometimes as the initial manifestations of the dysequilibrium syndrome (discussed later).

The risk of *cerebrovascular disease* is increased in patients undergoing dialysis and seems related to accelerated cerebrovascular disease and the high incidence of malnutrition, hypertension, diabetes, and hyperlipidemia among these patients. In one study, the high incidence of stroke resulted, at least in part, from inadequately treated hypertension. Presentation may be with hypertensive encephalopathy, posterior reversible encephalopathy syndrome (discussed earlier), transient ischemic attacks, or occlusive or hemorrhagic stroke. Infarcts may show a predilection for the vertebrobasilar arterial territory. Although stroke symptoms are common and are associated with cognitive and functional impairments, clinically significant stroke events are often unrecognized.

Intradialytic hypotension may complicate hemodialysis, and its frequent occurrence is often associated with high intradialytic weight gain and high ultrafiltration rates. Separately or together, these factors contribute to an increased cardiovascular morbidity and mortality observed in the hemodialysis population and increase the stroke risk. The use of lower concentrations of sodium in the dialysate reportedly helps to control or avoid some of these complications.[8]

The *osmotic demyelination syndrome* may occur after hemodialysis, leading clinically to convulsions, an alteration in the level of consciousness, and quadriparesis with hyperactive tendon reflexes and bilateral Babinski responses. MRI shows findings of demyelination in pontine and often extrapontine regions. The effects of dialysis on uremic encephalopathy and neuropathy have already been discussed, but dialysis may cause other neurologic disturbances that merit comment.

Sleep disturbances have a high prevalence in patients with end-stage kidney disease undergoing chronic hemodialysis. They include insomnia, obstructive sleep apnea, excessive daytime sleepiness, restless legs syndrome, and various parasomnias.

Entrapment Mononeuropathies

CARPAL TUNNEL SYNDROME

It was originally believed that carpal tunnel syndrome occurred because of increased venous pressure in the distal limb when an arteriovenous shunt had been placed for hemodialysis, the increased extravascular volume within the carpal tunnel or steal being held responsible for the median nerve compression. Carpal tunnel syndrome is diagnosed significantly more often on the side of an arteriovenous fistula than on the opposite side, and the duration of the fistula correlates with the development of the carpal tunnel syndrome. However, carpal tunnel syndrome is bilateral in about half of the patients.

The occurrence of β_2-microglobulin amyloidosis is probably more important etiologically in this context, particularly in patients on long-term hemodialysis. Amyloid fibrils have been isolated from amyloid-laden tissues inside the carpal tunnel and the protein identified as β_2-microglobulin. Circulating β_2-microglobulin presumably cannot be removed by conventional hemodialysis and accumulates in tissues; the consequent formation of amyloid fibrils appears to occur particularly in the region of the carpal tunnel, leading to carpal tunnel syndrome. A significant increase in carpal tunnel width and thickness in the palmoradiocarpal ligament, correlating with duration of long-term hemodialysis, has been found by ultrasound examination of the wrists of hemodialysis patients. The prevalence of carpal tunnel syndrome and the severity of symptoms have been improved by maneuvers to reduce the levels of β_2-microglobulin. Uremic tumoral calcinosis may also be responsible in some instances.

Treatment is as in other patients, with decompressive surgery if symptoms fail to respond to conservative measures.

ULNAR NERVE LESIONS

A high prevalence (between 41 and 60%) of ulnar neuropathy has been reported in patients receiving hemodialysis for end-stage renal disease. This may relate to arm positioning during hemodialysis, underlying polyneuropathy, upper-extremity vascular access, and uremic tumoral calcinosis.

Ischemic Neuropathy

A shunt for access during chronic hemodialysis and inserted between the radial artery and cephalic vein in the upper arm was reported by Bolton and colleagues to have caused an acute distal, ischemic neuropathy in two patients; electrophysiologic evidence was present of axonal degeneration of sensory fibers with mild ischemia, and of both motor and sensory nerve fibers with more severe ischemia.[9] This has been attributed to shunting of arterial blood away from the limb distally, with the nerves being selectively affected because of their greater vulnerability to ischemia. Other cases of this so-called *ischemic monomelic neuropathy* have since been reported, and the disorder is particularly likely in diabetics with renal failure and pre-existing peripheral vascular disease or neuropathy, although it may also occur in nondiabetic patients. Multiple upper-limb mononeuropathies develop, leading to burning pain and to sensory and motor deficits in the forearm and hand. Motor conduction block may be detected electrophysiologically shortly after the onset of symptoms, preferentially involving the median nerve, with clinical and electrophysiologic improvement following ligation or revision of the shunt. In some instances, onset is more insidious; more widespread signs of upper-extremity ischemia due to arterial steal are found distal to the fistula, such as established or impending tissue loss or nonhealing wounds.

In addition to arterial steal and venous hypertension syndromes, other complications of arteriovenous access for hemodialysis include high-output cardiac failure, pseudoaneurysm formation, hemorrhage, noninfectious fluid collections, acute forearm compartment syndromes, and access-related infections.

Dialysis Dysequilibrium Syndrome

Several neurologic disturbances may arise during or after hemodialysis, including headache, nausea, anorexia, muscle cramps, irritability, restlessness, agitation, confusion, coma, and seizures; increased intracranial pressure may lead to papilledema. Such symptoms tend to occur at the beginning of a dialysis program and were particularly conspicuous in the past when patients with advanced uremia were dialyzed aggressively. Patients now enter dialysis programs at an earlier stage of renal failure and the initial dialysis is started slowly with shortened dialysis times and less efficient dialysis, and this may account for the reduced incidence of the disorder, which seems more common in children and the elderly than in other age groups. Marked metabolic acidosis and the presence of other CNS disease may also be predisposing factors.[10]

Symptoms typically appear toward the end of a dialysis session, sometimes 8 to 24 hours later, and subside over several hours. When an agitated confusional state develops, it may persist for several days. Many patients manifest exophthalmos and increased intraocular pressure at the height of the syndrome, which may be helpful clinically for diagnostic purposes. Headache is the most common symptom reported by patients undergoing dialysis, and migrainous episodes may be precipitated during or after hemodialysis in patients with pre-existing migraine. Headache is otherwise usually diffuse and throbbing in quality. Subdural hematoma sometimes mimics the dysequilibrium syndrome and requires exclusion.

Movement of water into the brain leads to cerebral edema. According to the hypothesis known as the *reverse urea effect*, a rapid reduction in blood urea level lowers the plasma osmolality, thereby producing an osmotic gradient between blood and brain. Although urea is able to permeate cell membranes, this may take several hours to reach completion; accordingly, there is not enough time for urea equilibration when the blood urea level is reduced rapidly by hemodialysis. There is thus an influx of water into the cells. This results in increased intracranial pressure and cerebral edema. Alternatively or additionally, the osmotic gradient between brain and blood may not reflect simply the movement of urea; unidentified osmotically active substances ("idiogenic osmoles") are present in the brain of dialyzed uremic animals (but not dialyzed nonuremic animals) and have been incriminated. A decrease in cerebral intracellular pH, reflecting an increased production of organic acids that are osmotically active, may be important in this regard.[10]

A number of other disorders, such as uremic encephalopathy, intracranial infection or hemorrhage, cerebral infarction, hyponatremia, hypoglycemia, and medication-related encephalopathy must be excluded before the diagnosis is made with confidence. Prophylactic measures involve the gradual reduction in blood urea level by attention to the hemodialysis technique. In patients with established dialysis dysequilibrium syndrome, mild symptoms usually clear spontaneously over several hours, and symptomatic and supportive measures are all that are required; however, it may be necessary to slow or discontinue the dialysis session. Dialysis is stopped in patients with seizures or an altered level of consciousness and, if necessary, the plasma osmolality can be raised with either hypertonic saline or mannitol. Management is otherwise supportive, and improvement can be expected over the following day.

Wernicke Encephalopathy

Thiamine is a water-soluble vitamin that passes through dialysis membranes. However, dialysis does not remove more thiamine than is normally excreted in the urine, and no consistent change occurs after hemodialysis in plasma levels of the B vitamins. Wernicke encephalopathy has occurred in patients on chronic dialysis, but is relatively infrequent. It has been related to anorexia, vomiting, a diet low in thiamine-containing foods, and intravenous alimentation without thiamine supplementation; other potential causes in uremia are infections that may stress thiamine reserves and the use of repeated infusions of glucose, insulin, and bicarbonate to lower the serum potassium level.

Among patients undergoing dialysis in whom Wernicke encephalopathy develops in the absence of alcoholism or other precipitating factors and is diagnosed at autopsy, ophthalmoplegia may be evident in only occasional instances, but in other cases the full triad of ophthalmoplegia, ataxia, and an altered level of consciousness is encountered. Hypothermia is common. Intravenous administration of thiamine reverses the clinical deficit. Given the reversible nature of the disorder, it is important to consider it in all patients on hemodialysis who exhibit at least one of its classic features; dialysis dysequilibrium syndrome, dialysis dementia, and uremic encephalopathy have each been diagnosed erroneously in patients who were subsequently found to have Wernicke encephalopathy. Indeed, in one series of 30 consecutive patients on regular hemodialysis or peritoneal dialysis who were admitted with an alteration in mental status, 10 had an unexplained encephalopathy after initial evaluation and were eventually found to have thiamine deficiency; nine responded to thiamine supplementation and one died.[11]

Dialysis Dementia

Clinical Aspects

There has been a decline in the incidence of this progressive encephalopathy, which may occur in patients undergoing long-term dialysis. The first symptom is often a stammering hesitancy of speech that eventually progresses to speech arrest, dysarthria, and expressive aphasia. The speech disorder is intensified during and immediately after dialysis and initially may occur only at these times. Other manifestations such as tremor, myoclonus, asterixis, seizures, and dementia become apparent as the disorder advances, and hallucinations and delusional thinking round out the clinical picture. Focal neurologic abnormalities are found occasionally. Symptoms initially occur immediately after dialysis and then clear, but eventually they fail to resolve and the patient becomes increasingly demented. The EEG shows abnormal bursts of high-voltage slow activity and spikes anteriorly. The CSF is normal. The differential diagnosis includes other causes of dementia, but metabolic encephalopathy and structural lesions such as subdural hematoma, normal-pressure hydrocephalus, hypertensive encephalopathy, multi-infarct dementia, and stroke require exclusion.

Pathogenesis

A clustering of cases in areas with aluminum-contaminated water was noted originally, and water-purification measures have led to a substantial reduction in the incidence of the disorder. The disorder results from accumulation of aluminum in the brain and is now rarely encountered because of elimination of aluminum in the dialysate. Phosphate retention occurs in renal failure, leading eventually to hyperparathyroidism, and reduction of the serum phosphate concentration with phosphate binders is therefore important. The substitution of phosphate binders such as calcium carbonate and calcium acetate, and of nonmineral-containing phosphate binders, for oral aluminum-containing phosphate binders has also been important in reducing the aluminum content in the brain. The toxicity of aluminum may involve disruption of the inositol phosphate system and calcium regulation, facilitation of oxidative injury, and disruption of basic cell processes.

Treatment

Diazepam is initially helpful in treating the myoclonus and seizures and in improving speech, but it is less effective later. Increased dialysis time and renal transplantation have not altered the natural history. In untreated patients, death usually occurs within a year of the onset of symptoms. The chelator deferoxamine can remove excess aluminum and thereby reverse acute encephalopathy, as well as the osteomalacia and anemia that may also be associated with aluminum overload. However, its introduction may be associated with visual and auditory toxicity and with increased neurologic and other side effects from acute aluminum toxicity (presumably because of the rapid mobilization of stored aluminum) in occasional patients; some patients have developed a rapidly progressive and fatal systemic or rhinocerebral mucormycosis. Experimental studies in animals suggest that deferoxamine enhances the pathogenicity of the responsible organism and reduces the effectiveness of treatment with amphotericin. Nevertheless it is the mainstay of treatment for established dialysis dementia.

Several protocols for the administration of deferoxamine have been proposed. A baseline serum aluminum level is determined: normal levels are 6 ± 3 μg/L, but excess aluminum deposition is unlikely when values are less than 20 μg/L. If baseline levels exceed this, a low-dose deferoxamine test is performed by administering 5 mg/kg 1 hour before the end of dialysis if aluminum overload (serum aluminum levels of 60 to 200 μg/L) is present or toxicity is suspected clinically. If this increases serum aluminum by 50 μg/L or more when measured 2 days after the deferoxamine, the test is considered positive. For treatment purposes, deferoxamine can be given to symptomatic patients once weekly in the last hour of a dialysis session; however, to avoid the risk of deferoxamine neurotoxicity, it is not given to patients with serum aluminum levels exceeding 120 μg/L until the level is first lowered by withdrawal of aluminum exposure. This is because deferoxamine may cause severe, sometimes fatal, complications when administered to patients with very high serum aluminum concentrations. When serum levels exceed 200 μg/L, the deferoxamine test should not be performed; instead, daily hemodialysis using high-flux membranes and a low dialysate aluminum concentration, and withdrawal of all aluminum-containing oral agents, is necessary. A low-dose deferoxamine test (5 mg/kg) is given after 4 to 6 weeks of such treatment (if serum levels are <200 μg/L) to determine the timing of further treatment. National and society guidelines should be consulted for further details.

The length of treatment required is uncertain, but it may need to be for many months. Many cases of dialysis dementia have been stabilized or improved by deferoxamine. The need for treatment is unclear in patients with an asymptomatic increase in aluminum levels.

COMPLICATIONS OF TRANSPLANTATION

Various neurologic complications are caused by the neurotoxicity of immunosuppressive agents, as discussed in Chapter 44. When acute rejection encephalopathy occurs, patients experience headache, confusion, and seizures, sometimes accompanied by papilledema, increased CSF pressure, and computed tomography (CT) evidence of diffuse cerebral edema. The EEG is diffusely slowed and may show focal features. Treatment of the rejection episode leads to improvement.

Femoral and Related Neuropathy

Femoral neuropathy is a common complication of renal transplantation in the iliac fossa, occurring ipsilateral to the transplant surgery with an incidence on the order of 2 percent. Nerve compression typically occurs intraoperatively, for example, with prolonged use of retractors. When compression leads to neurapraxia, recovery is likely to be rapid and complete, as in most patients; severe compression or nerve ischemia leads to axonal loss, delayed recovery, and residual deficits. In patients undergoing renal transplantation involving either the internal or external iliac artery, sensory disturbances may be the sole manifestation and are not necessarily confined to the territory of the femoral nerve: in one series of 20 patients in which the internal iliac artery was used, for example, sensory complaints were in the anterior thigh in 15, lateral thigh in 3, and anterolateral thigh in 2,[12] suggestive of involvement of the lateral femoral cutaneous nerve.

Development of Malignant Disease

The rates of malignancies among 35,765 first-time recipients of deceased or living donor kidney transplantations between 1995 and 2001 was examined by Kasiske and associates using Medicare billing claims.[13] For common tumors, such as of the colon, lung, prostate, stomach, esophagus, pancreas, ovary, and breast, cancer rates were approximately twice as high after kidney transplantation as in the general population. Melanoma, leukemia, hepatobiliary tumors, cervical, and vulvovaginal tumors were each increased about 5-fold; testicular and bladder cancers about 3-fold; kidney cancer (typically of the native kidney) 15-fold; and Kaposi sarcoma, non-Hodgkin lymphomas, and nonmelanoma skin cancers more than 20-fold. Thus, cancer screening and attention to prophylactic measures are important after kidney transplantation. The development of such neoplasms may involve the nervous system

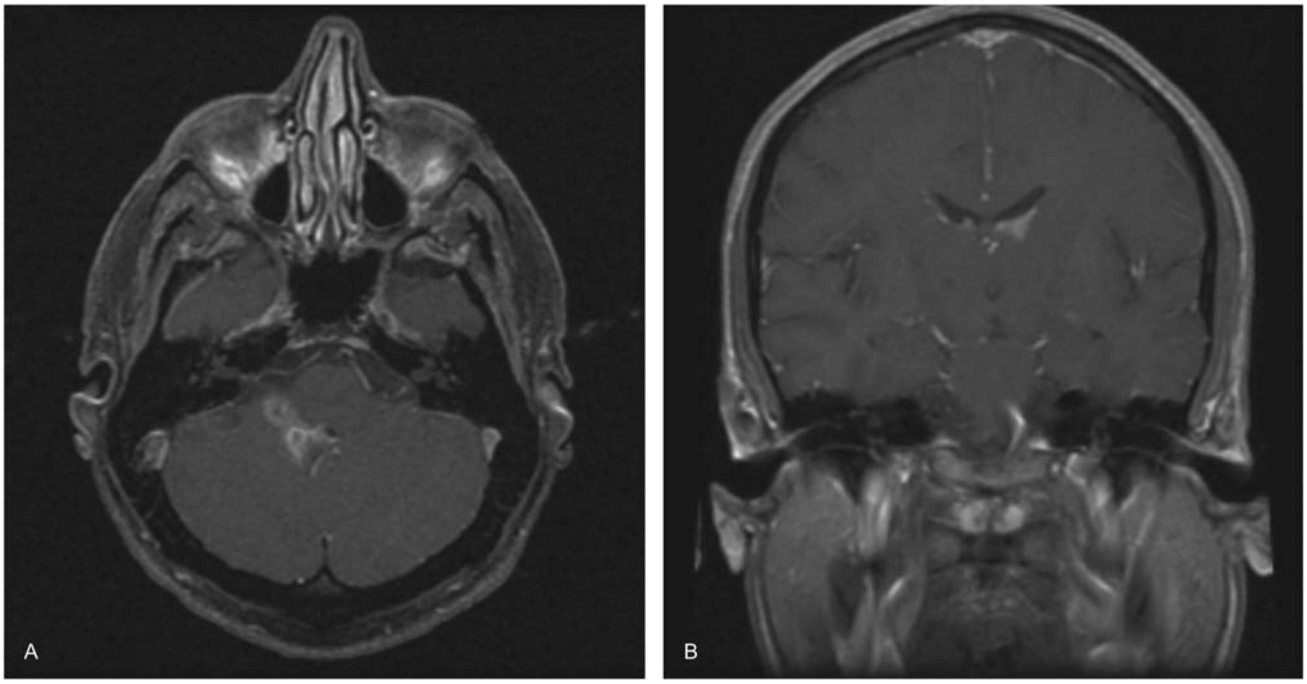

FIGURE 16-4 ■ *A*, Axial postcontrast T1-weighted MRI demonstrates an enhancing mass located in the right lateral recess of the fourth ventricle. *B*, Coronal postcontrast T1-weighted image shows an enhancing subependymal mass involving the left lateral ventricle. The findings are most consistent with CSF spread of lymphoma. (Courtesy of William P. Dillon, MD, University of California, San Francisco.)

directly by metastatic spread, may lead to a paraneoplastic syndrome, or may produce secondary neurologic abnormalities as a consequence of treatment (Chapters 26, 27, and 28).

Brain Tumors

Non-Hodgkin lymphoma constitutes more than 90 percent of lymphomas in transplant recipients. Most of these lymphomas are of the B-cell type and follow B-cell proliferation related to infection with Epstein–Barr virus in patients who are chronically immunosuppressed. Extranodal involvement after organ transplantation occurs commonly and—in almost one-quarter of patients—involves the CNS (Fig. 16-4). Involvement of the transplanted kidney may also occur, causing renal failure. The degree of immunosuppression, age (greater in those younger than 25 years), time since transplant (greater in the first year), race (greater in Caucasians than in African Americans), and serologic status regarding Epstein–Barr virus infection influence the risk of disease. The development of mental status changes or new neurologic abnormalities should raise concern about the possibility of CNS involvement. Imaging studies (CT or MRI) of the head, CSF analysis for Epstein–Barr virus and cytologic examination for malignant cells, and brain biopsy generally lead to the diagnosis. MRI may underestimate the extent of the tumor. The use of corticosteroids, which alter the imaging and histopathologic findings, may confound interpretation of imaging studies.

The incidence of *primary CNS lymphoma* is increasing, especially among the elderly. The tumor is located supratentorially in more than two-thirds of instances and typically is periventricular and involves deep subcortical structures such as the basal ganglia and corpus callosum (Fig. 16-5); subependymal spread is common. Abnormal lymphocytes may disseminate along CSF pathways and subsequently spread throughout the CNS. The eye may also be involved. As with systemic lymphoma, the high incidence of primary CNS lymphoma in transplant recipients receiving immunosuppressants indicates involvement of the immune system in its pathogenesis and, again, the Epstein–Barr virus may have a role. Presenting symptoms depend on the location of the lesion. Supratentorial lesions may cause headaches (sometimes from increased intracranial pressure or meningeal involvement), personality

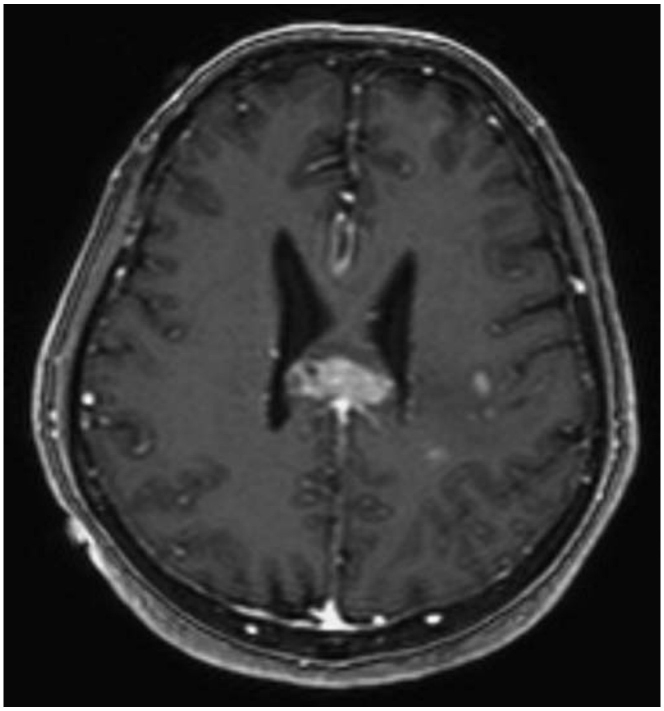

FIGURE 16-5 ■ MRI of a patient with biopsy-proven primary lymphoma of the brain. Axial postcontrast T1-weighted MRI shows an enhancing mass involving the splenium of the corpus callosum as well as two satellite nodules within the white matter of the left posterior frontal lobe. (Courtesy of William P. Dillon, MD, University of California, San Francisco.)

changes, cognitive abnormalities, blurred vision, or focal motor or other deficits. Convulsions are relatively uncommon. Cranial neuropathies, ataxic syndromes, and other signs of brainstem involvement occur with infratentorial intracranial involvement. Meningeal involvement is relatively common as the disease advances and leads to multifocal disease with cranial and spinal neuropathies, headaches, signs of meningeal irritation, and, occasionally, hydrocephalus. In rare instances of primary spinal involvement, there is weakness, sensory loss, and sphincter dysfunction, depending on the site and extent of the lesion. Spinal lesions are more often intramedullary, whereas in patients with systemic lymphoma diffuse leptomeningeal involvement or extradural nodules are more likely. Recurrence is usually within the brain, but systemic dissemination occurs occasionally and tends to involve extranodal organs, such as kidneys or skin.

The CSF usually shows nonspecific findings, but cytology may reveal malignant cells, especially if repeated examinations are performed. The absence of such cells does not exclude the diagnosis. CT usually shows a mass much larger than that suggested by the clinical findings; there are usually isodense, hyperdense, and hypodense areas, with contrast enhancement. On T2-weighted MRI, the mass may appear isointense to hypointense, enhances homogeneously with contrast administration, may be associated with extensive edema, is often in contact with the subarachnoid space, and typically is without necrosis. One-third of these tumors are multifocal. Tumors may be missed by one imaging modality and detected by the other; both may miss meningeal disease. MRI or myelography detects spinal disease. A definitive diagnosis is made by histopathologic examination after stereotactic biopsy. Extensive resection of the tumor is usually not attempted given its deep location and often multifocal nature and because of the high surgical morbidity.

Surgery has no role in treatment. Treatment is with high-dose methotrexate in combination with other chemotherapeutic agents and rituximab. Subsequent consolidation therapies have included whole-brain radiotherapy and autologous stem-cell transplantation. The efficacy of immunotherapy for salvage therapy is under study.

Central Nervous System Infections

In renal transplant recipients, the risk of infections (and neoplasia), with their attendant mortality and morbidity, increases with increasing immunosuppression rather than with the use of a specific immunosuppressive agent. It is important to bear this in mind when the addition of a potent immunosuppressive agent is under consideration for the treatment of acute rejection episodes. The risk of infection is also influenced by environmental exposure, by the presence of indwelling catheters that may serve as a conduit for infection, and by whether peritoneal dialysis rather than hemodialysis was utilized prior to transplantation (as the former is associated with a higher risk of infection). Other factors that bear on the issue are co-existing diseases such as diabetes that render patients more prone to infection, poor nutritional status, metabolic abnormalities such as uremia, and infection with immunomodulating viruses such as Epstein–Barr and human immunodeficiency virus.

CNS infections are an important consideration in transplant recipients. When acute meningitis occurs, it is usually caused by *Listeria monocytogenes*, whereas subacute or chronic meningitis is commonly caused by *Cryptococcus neoformans*, although systemic infection with *Mycobacterium tuberculosis*, *L. monocytogenes*, *Histoplasma capsulatum*, *Nocardia asteroides*, and certain other organisms may have a similar presentation. Signs of meningeal irritation may be subtle or absent because of the anti-inflammatory effects of immunosuppressants. Fever, headache, and impairment of consciousness may also be due to CNS lymphoma, which must therefore be distinguished, as described earlier. The presence of unexplained fever and headache in transplant recipients mandates brain imaging by CT scan or MRI and examination of the CSF. Brain abscesses (Fig. 16-6) are well described in transplant recipients and, in most instances, the primary source of infection is the lung. CT of the chest is therefore important, especially when chest radiographs are normal or unhelpful, for diagnostic purposes in differentiating fungal brain abscess from brain tumor in transplant recipients. *Aspergillus* has a predilection for dissemination to the brain and accounts for most fungal brain abscesses; such fungal infections usually lead to multiple brain abscesses and have a poor prognosis. Abscess may also result from *L. monocytogenes*, *Toxoplasma gondii*, or *N. asteroides*. With *Listeria* infection, abscesses are also commonly multiple, with a high mortality. The clinical presentation is often with neurologic deficits or seizures of abrupt onset or with a worsening confusional state. The CT scan may show poorly circumscribed, low-absorption areas with minimal or no contrast enhancement and little mass effect. MRI shows ring-enhancing lesions with surrounding edema; distinction from tumor is sometimes difficult, but diffusion-weighted imaging is helpful in this regard. The CSF may be unrevealing. Brain biopsy is sometimes the only reliable way to establish a diagnosis. Treatment is discussed in later chapters.

Progressive multifocal leukoencephalopathy (Fig. 16-7) due to JC virus infection has been described in transplant recipients and leads to cognitive changes, seizures, and focal neurologic deficits. In one reported case, immunosuppression was discontinued and the patient returned to hemodialysis; his neurologic symptoms and imaging abnormalities gradually resolved completely. Similar clinical deficits may relate to other viral infections, such as herpes simplex or Epstein–Barr virus, or may reflect toxicity of immunosuppressants such as cyclosporine or tacrolimus.

West Nile virus infection manifests similarly in transplant recipients as in other patients, but neurologic damage tends to be especially severe.

HEREDITARY DISORDERS OF THE NERVOUS SYSTEM AND KIDNEYS

Various uncommon inherited disorders affect both the kidneys and the nervous system, meriting brief discussion here.

Fabry Disease

Fabry disease is an X-linked lysosomal storage disease resulting from deficiency of ceramide trihexosidase (α-galactosidase), which catalyzes the hydrolytic cleavage of the terminal galactose from globotriaosylceramide. It relates to mutations of the α-galactosidase A (*GLA*) gene at Xq22. Presentation may be at any age.[14]

A small-fiber neuropathy leads to severe neuropathic or limb pain and dysautonomic symptoms, such as hypohidrosis and fever. Vascular skin lesions (angiokeratomas) and corneal opacities occur, and renal, cardiac, endocrine, and other organ involvement results from glycosphingolipid accumulation. Renal involvement leads to proteinuria, polyuria, and polydipsia; progressive renal failure typically develops in adulthood. Kidney function is worse in patients with undetectable α-galactosidase activity compared to those with some residual activity.

Cerebrovascular involvement is associated with transient ischemic attacks and strokes, with the vertebrobasilar circulation being symptomatic most often. Elongated, ectatic, tortuous vertebral and basilar arteries are common angiographic and pathologic findings. The MRI may show focal or multifocal white matter lesions in affected males and in female carriers, and these may reflect an underlying vasculopathy. A fatal outcome is common in middle life from uremia or cerebrovascular disease.

Management involves the administration of enzyme replacement therapy with agalsidase alfa or agalsidase beta. This helps to reduce—but often does not eliminate—neuropathic pain. Treatment of the pain with gabapentin, carbamazepine, or amitriptyline may be helpful. Nonsteroidal anti-inflammatory agents are usually ineffective, and narcotics are best avoided. Enzyme replacement therapy also helps to improve sensory thresholds over the long term, but the effect of such treatment on CNS manifestations—and especially on stroke risk—is unclear. Antiplatelet agents are therefore required to lessen the risk of stroke.

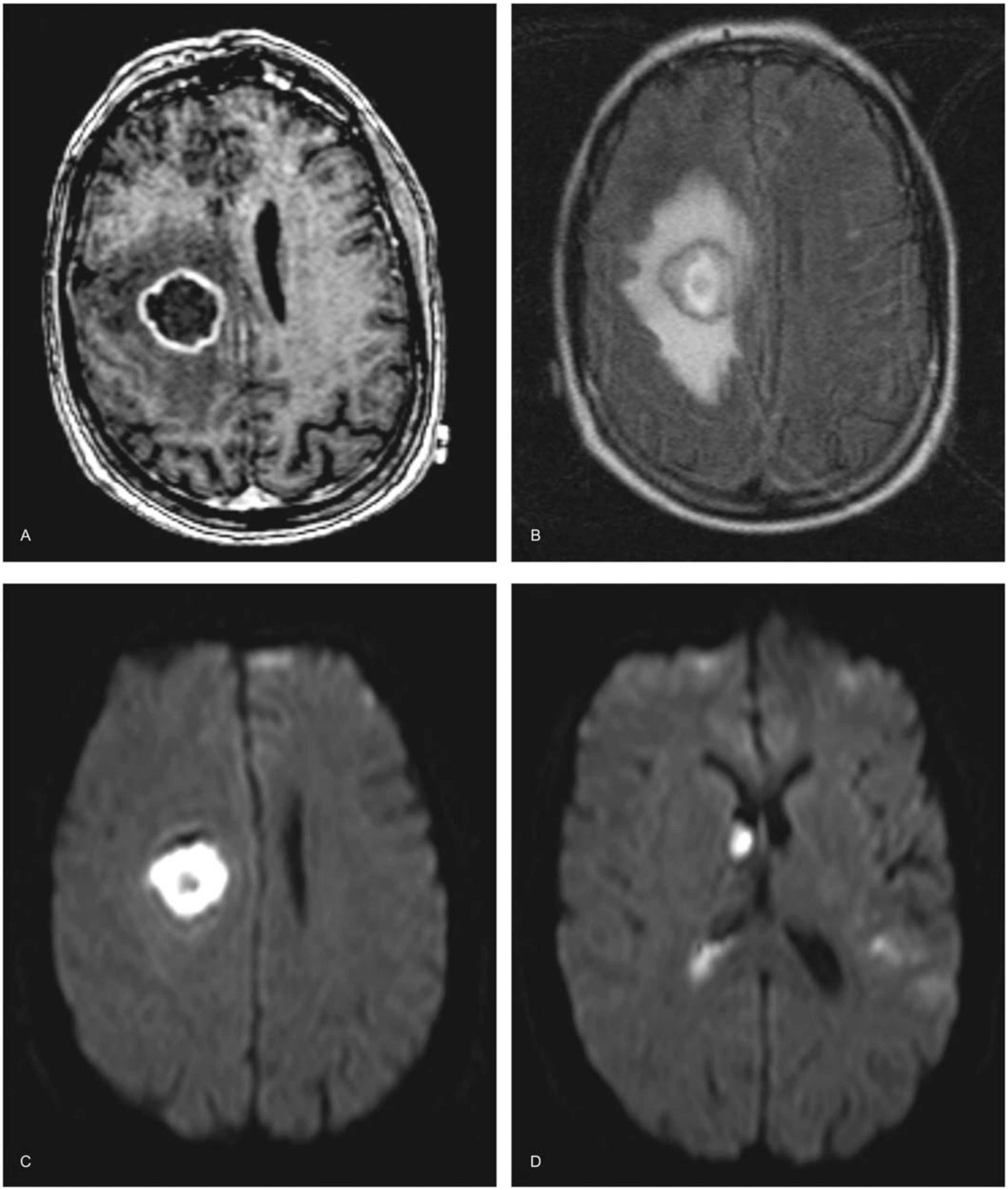

FIGURE 16-6 ■ *A*, Axial postcontrast T1-weighted image demonstrates a ring-enhancing mass lesion in the right frontal lobe with surrounding vasogenic edema. *B*, Axial T2-weighted FLAIR image demonstrates a mass surrounded by a zone of increased signal intensity consistent with vasogenic edema. The mass itself consists of several layers of abnormal signal. Within the center of the mass, a zone of lower signal is seen, surrounded by alternating zones of higher and lower signal. The capsule of the mass shows low signal and is the area that enhances with contrast material (see *A*). *C*, Axial diffusion-weighted image. The central portion of the mass shows high signal, consistent with restricted diffusion. The appearance of a ring-enhancing mass containing material with restricted diffusion is most consistent with a cerebral abscess. *D*, Axial diffusion-weighted image at the level of the lateral ventricles shows abnormal high-signal layering within the right lateral ventricle and in the sulci of the left hemisphere, consistent with both meningeal and intraventricular extension of abscess material. (Courtesy of William P. Dillon, MD, University of California, San Francisco.)

The decline in renal function may be slowed by enzyme replacement therapy and also responds to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Kidney transplant is sometimes necessary.

von Hippel–Lindau Disease

In autosomal-dominantly inherited von Hippel–Lindau disease, the responsible gene maps to chromosome 3p25 and is a tumor suppressor gene. Genetic screening can be performed when the diagnosis is suspected. Renal cysts and cancers occur in patients with CNS and retinal hemangioblastomas (often bilateral), and sometimes with pancreatic cysts and pheochromocytoma. The CNS hemangioblastomas commonly involve the cerebellar hemispheres and may be asymptomatic; spine and brainstem lesions are also well described (Fig. 16-8). A variety of visual complications may occur, mandating the need for regular ophthalmologic screening. Monitoring for the development of renal lesions by CT scan and ultrasound, and for CNS lesions by gadolinium-enhanced MRI of the entire neuraxis, also is important. Treatment is surgical or by radiation therapy.

Polycystic Kidney Disease

At least two different genetic loci for autosomal-dominant polycystic kidney disease have been identified (16p13 and 4q21). The renal manifestations of this disorder include hypertension, urinary tract infection, polyuria, hematuria, nephrolithiasis, pain in the flank, and progressive renal failure. Hypertension also may occur in relation to the kidney disease.

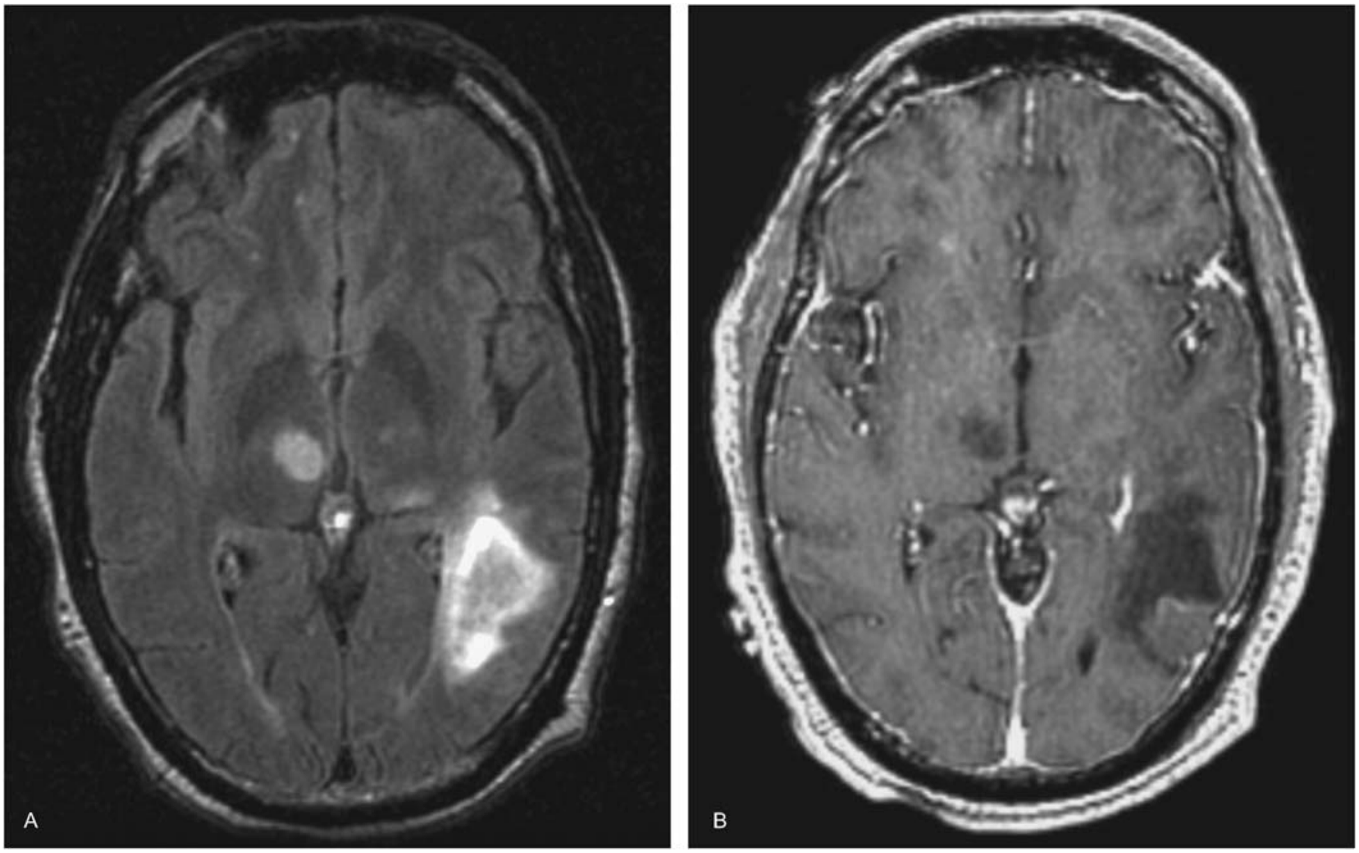

FIGURE 16-7 ■ *A*, An immunosuppressed patient with alteration of mental status. Axial T2-weighted fluid-attenuated inversion recovery MRI demonstrates several discrete areas of T2 prolongation involving the right and left thalamus and the left posterior frontotemporal area. Despite the large size of the lesion, no mass effect is present. *B*, Axial postcontrast T1-weighted image demonstrates well-circumscribed low-intensity lesions without contrast enhancement. Subsequent brain biopsy confirmed the diagnosis of progressive multifocal leukoencephalopathy. (Courtesy of William P. Dillon, MD, University of California, San Francisco.)

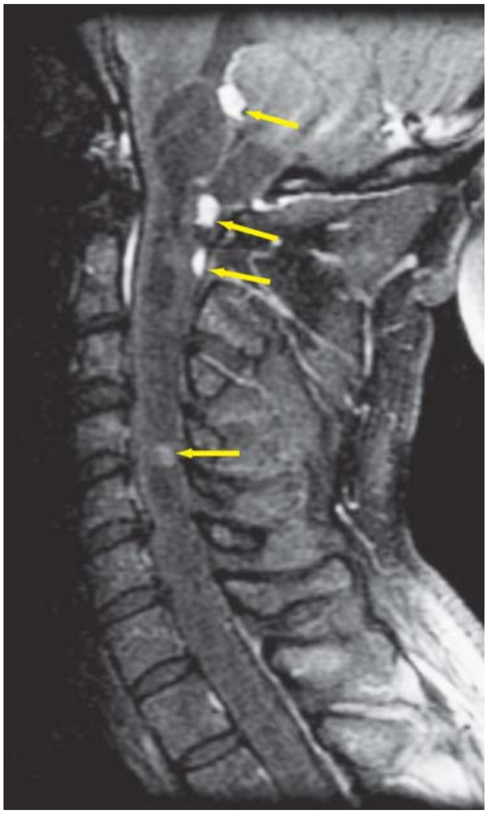

FIGURE 16-8 ■ Sagittal postcontrast T1-weighted image through the cervical spinal cord and lower cerebellum demonstrating several intensely enhancing pial-based hemangioblastomas (*arrows*) associated with nonenhancing cysts. (Courtesy of William P. Dillon, MD, University of California, San Francisco.)

Intracranial arterial aneurysms, sometimes multiple and unrelated to the occurrence of hypertension, are associated, occurring in between 5 and 20 percent of patients depending on age. Aneurysmal rupture, which occurs especially in older subjects and those with large aneurysms, may lead to subarachnoid or intracerebral hemorrhage. In a retrospective study of 77 patients from 64 families with ruptured (71 instances) or unruptured (6) aneurysms, mean age at the time of rupture was 39.5 years (range, 15 to 69 years), renal function was normal in half of the patients, and 11 percent were on renal replacement therapy. The ruptured aneurysm was usually located on the middle cerebral artery; in 31 percent of the patients, additional intact aneurysms were found. On long-term follow-up, 27 (38%) were left with severe disability. Five patients bled from another aneurysm 2 days to 14 years after initial rupture.[15] Treatment of ruptured aneurysms is as for aneurysmal subarachnoid hemorrhage occurring for other reasons, involving emergency CT scanning, four-vessel angiography, and surgery or endovascular treatment. The indications for surgical or other treatment for unruptured aneurysms are the same as in patients without polycystic kidney disease.

Screening of patients with autosomal-dominant polycystic kidney disease by MR angiography or high-resolution CT angiography at periodic intervals for the presence of cerebral aneurysms is probably worthwhile, at least in high-risk patients, such as those with previous aneurysmal rupture or a positive family history of an intracerebral bleed, but no clear guidelines exist for the frequency with which this should be undertaken. The value of widespread screening for intracranial aneurysms in patients with polycystic kidneys has otherwise been questioned because most intracranial aneurysms detected by presymptomatic screening in this population are small, and follow-up studies do not suggest an increased risk of growth and rupture, compared to intracranial aneurysms in the general population.

Other Hereditary Disorders

Alport syndrome (hereditary nephritis) is a genetically heterogeneous disorder with autosomal dominant or recessive or an X-linked pattern of inheritance. Patients develop progressive glomerular disease leading eventually to end-stage renal disease, and—especially in the X-linked and recessive forms—ocular abnormalities (affecting the retina, cornea, or lens) and bilateral sensorineural hearing loss. Aortic aneurysms may occur. Diagnosis is usually based on the history and family background, supported by biopsy or genetic testing. There is no specific treatment.

Psychomotor retardation and developmental delay occur in the X-linked recessive *Lowe syndrome* (in which there is progressive renal impairment) and autosomal recessive *Bartter syndrome* (in which ionic resorption is impaired in the loop of Henle). Cerebellar ataxia is a feature of *Hartnup disease*, in which there is impaired renal resorption of amino acids leading to aminoaciduria. In *Joubert syndrome* of cerebellar (vermian) and brainstem maldevelopment, multicystic renal dysplasia and chronic kidney disease may be conjoined.

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CHAPTER

17

Neurologic Complications of Electrolyte Disturbances

AMAR DHAND

SODIUM
- Hyponatremia
  - *Subarachnoid Hemorrhage and Other Intracranial Diseases*
  - *Central Pontine Myelinolysis (Osmotic Myelinolysis)*
- Hypernatremia

POTASSIUM
- Hypokalemia
- Hyperkalemia

CALCIUM
- Hypocalcemia
- Hypercalcemia

MAGNESIUM
- Hypomagnesemia
- Hypermagnesemia

Electrolyte disturbances are frequent and associated with a variety of central and peripheral neurologic manifestations. Electrolyte disturbances are usually secondary processes related to a primary metabolic or endocrine disorder. Effective management requires prompt identification and treatment of the underlying primary disorder, and correction of the electrolyte abnormality. Neurologic consequences of electrolyte disorders are usually functional rather than structural. Consequently, the neurologic manifestations of electrolyte disturbances are often reversible, particularly if corrected and effectively managed at an early stage. The neurologic manifestations of abnormalities of serum sodium, potassium, calcium, and magnesium are reviewed.

SODIUM

Extracellular fluid volume is directly dependent on total body sodium, the principal osmotic component of that fluid compartment. Consequently, most patients with hyponatremia are also hypo-osmolar, and those with hypernatremia are hyperosmolar. The symptomatic neurologic manifestations of serum sodium abnormalities typically involve the central, rather than the peripheral, nervous system. Neurologic manifestations are generally the consequence of hypo-osmolarity in hyponatremia and hyperosmolarity in hypernatremia. Slow changes to sodium, even to extreme values, infrequently produce symptoms due to the brain's adaptation to serum osmolality. Rapid sodium change, up or down, produces characteristic neurologic symptoms.

Hyponatremia

Hyponatremia is defined as a serum sodium level of less than 135 mEq/L. It is most often associated with hypo-osmolarity and is classified into three categories based on whether extracellular fluid volume is decreased, normal, or increased. *Hypo-osmolar hyponatremia with hypovolemia* results from renal sodium loss (e.g., from diuretic usage, mineralocorticoid deficiency, salt-losing nephropathy, or osmotic diuresis) or extrarenal sodium loss (e.g., from vomiting, diarrhea, or third-space losses). *Hypo-osmolar hyponatremia with normovolemia* (no edema) results from conditions such as the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), glucocorticoid deficiency, hypothyroidism, and stress. It can also occur in response to various drugs, including carbamazepine and psychotropic

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agents. *Hypo-osmolar hyponatremia with excess extracellular fluid* (edema) occurs in conditions such as cirrhosis, cardiac failure, nephrotic syndrome, and acute or chronic renal failure. Other less common variants include *hyponatremia with normal osmolarity* (pseudohyponatremia), which occurs in the setting of hyperlipidemia or hyperproteinemia, and *hyponatremia with hyperosmolarity*, which occurs in the setting of hyperglycemia.

The separation of hypo-osmolar hyponatremia into these three categories based on the extracellular fluid volume status has therapeutic implications. In normovolemic and hypervolemic hypo-osmolar hyponatremia, the fundamental principle of therapy is water restriction. In hypovolemic hypo-osmolar hyponatremia the basis of therapy is replacement of water and sodium (generally with isotonic saline or lactated Ringer solution). Overall, the rate of sodium correction should be no more than 6 to 12 mEq/L in the first 24 hours.

Among hospitalized patients, hyponatremia is the most common electrolyte abnormality that occurs. Hyponatremia is associated with increased risk of death, more likely discharge to short- or long-term care facility, and longer length of stay.[1] However, these associations may reflect the seriousness of underlying disorders rather than the hyponatremia itself.[2]

Neurologic symptoms related to hyponatremia are seen much more frequently in patients with acute, rather than chronic, hyponatremia. For example, a serum sodium concentration of 130 mEq/L might produce neurologic symptoms if it developed rapidly, whereas a serum sodium concentration of 115 mEq/L might be asymptomatic if it developed very slowly. An alteration in mental status is the most common neurologic manifestation of hyponatremia and ranges from mild confusion to coma. Patients with underlying neurodegenerative disorders and those of advanced age are particularly susceptible to delirium from even small changes in serum sodium. This hyponatremic encephalopathy may be associated with nonspecific generalized slowing on the electroencephalogram. As the level of serum sodium decreases, the risk of seizures increases. The occurrence of convulsions in the setting of acute hyponatremia (typically with a serum sodium concentration less than 120 mEq/L) can portend a high mortality rate. The occurrence of seizures in patients with acute hyponatremia represents a medical emergency and necessitates rapid, but only partial, correction of the serum sodium concentration. Control of hyponatremic seizures can be obtained by the judicious use of 3 percent saline (4 to 6 mL/kg) in an attempt to raise the serum sodium concentration by small 3 to 5 mEq/L increments.[3] When hypertonic saline is used, it is prudent to check the serum sodium levels every 2 to 4 hours.

Occasionally, focal neurologic signs and symptoms are seen in the setting of hyponatremia and include hemiparesis, monoparesis, ataxia, nystagmus, tremor, rigidity, and aphasia. These focal abnormalities can represent aggravation of an underlying structural lesion and often remit with resolution of the hyponatremia. Such focal deficits require neuroimaging even if they fully resolve with sodium correction. The central nervous system (CNS) manifestations of acute hyponatremia are related to cerebral edema and displacement of brain amino acids, although mechanisms are being studied. Although occasional muscle twitches, fasciculations, and cramps may be seen in acute hyponatremia, muscle symptoms are not common.

Hyponatremia associated with limbic encephalitis is characteristic of anti-LGI1 encephalitis.[4] Patients with this disorder also present with faciobrachial dystonic seizures. This form of voltage-gated potassium channel encephalitis is important to recognize in order to promptly initiate anti-inflammatory therapies.

SUBARACHNOID HEMORRHAGE AND OTHER INTRACRANIAL DISEASES

Hyponatremia frequently develops in patients with subarachnoid hemorrhage. There is controversy on whether hyponatremia is associated with symptomatic cerebral vasospasm and cerebral infarction. One classic study of 134 patients showed that 27 out of 44 patients who developed hyponatremia also developed cerebral infarctions. The authors emphasized that fluid restriction, the typical strategy to treat SIADH, was dangerous in these patients.[5] Guidelines have cited this evidence in describing a link between hyponatremia and morbidity in subarachnoid hemorrhage. However, recent studies have shown contradictory results. In one study of 198 patients, hyponatremia was not associated with worse neurologic outcomes.[6] Rather, patients with sodium variability of or exceeding 6 mEq/L had increased cerebral infarction and worse functional outcomes. These fluctuations may occur in patients with either hyponatremia or hypernatremia. Further study in larger cohorts of patients is needed to understand the involved mechanisms.

Therapeutically, hyponatremia is typically treated with oral or intravenous sodium repletion in an attempt to restore or maintain normovolemia. Fluid restriction in patients with subarachnoid hemorrhage is discouraged because these patients usually do not have SIADH. Rather, their hyponatremia is more likely to be due to cerebral salt wasting. In a prospective study of 21 patients with aneurysmal subarachnoid hemorrhage, plasma volume decreased by more than 10 percent in 11 of the patients.[7] Serum sodium decreased in 9 of the 21 patients. Plasma volume decreased by more than 10 percent in 6 of 9 patients with hyponatremia, and a similar decrease occurred in 5 of 12 patients with normal serum sodium. Eight of the 9 patients with hyponatremia had a negative sodium balance, whereas only 4 of the 12 patients with normal serum sodium had a negative sodium balance. Finally, 10 of the 12 patients with a negative sodium balance had a decrease in plasma volume exceeding 10 percent. Therefore, fluid restriction instituted to correct hyponatremia attributed to presumed SIADH may exacerbate an already volume-depleted state and subject patients to a greater risk of ischemic cerebral damage from vasospasm.

CENTRAL PONTINE MYELINOLYSIS (OSMOTIC MYELINOLYSIS)

Central pontine myelinolysis was recognized as a distinct clinical entity in 1959 in four cases, occurring on a background of alcoholism and malnutrition. Its pathologic features involve a symmetric noninflammatory demyelination in the base of the pons with relative sparing of neurons and axons. The classic clinical presentation includes pseudobulbar palsy and spastic quadriparesis. Following the original description, many additional cases were reported in rapid succession, suggesting that central pontine myelinolysis is not a rare disorder. Many cases were not associated with alcoholism or malnutrition. It may, for example, occur in subjects with extensive burns or liver transplants. By 1964, the relatively high frequency of subclinical lesions (Fig. 17-1) was noted, and this was validated by many subsequent reports. The history of the recognition and pathogenesis of central pontine myelinolysis has been summarized elsewhere.[7]

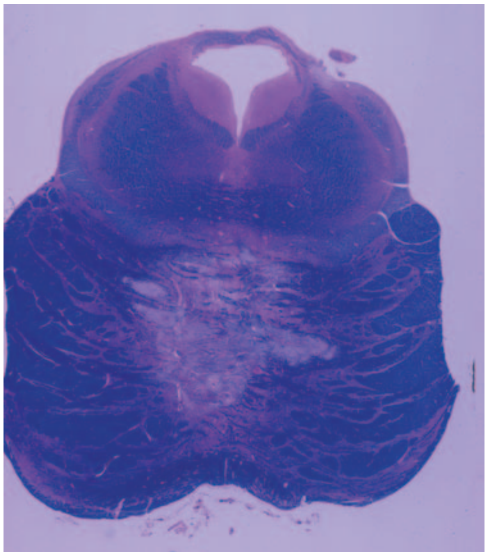

FIGURE 17-1 ■ Macrosection of the pons demonstrating central demyelination, an incidental finding of subclinical central pontine myelinolysis in a patient with a history of electrolyte abnormalities and diuretic use (Luxol fast blue).

Rapid sodium correction of more than 12 mEq/L per day causing central pontine myelinolysis was popularized by a paper published in 1986.[8] Sterns and colleagues noted neurologic complications in eight patients whose serum sodium had been corrected by more than 12 mEq/L per day. Conversely, patients with hyponatremia that was corrected more slowly made uncomplicated recoveries. In a review of the literature, those authors found 80 patients with severe hyponatremia (less than 106 mEq/L). Of these 80 patients, enough detail was reported in 51 to determine a maximal rate of correction of serum sodium. In 39 of 51 patients who were corrected rapidly (greater than 12 mEq/L per day), 22 (58%) had some type of neurologic complication. Of these 22 patients, 14 (64%) were suspected of having central pontine myelinolysis. Of the 13 patients who were corrected slowly (less than 12 mEq/L per day), none experienced a neurologic complication. The authors concluded that the risk of central pontine myelinolysis was greatest in patients with chronic hyponatremia, where a judicious correction strategy should be employed. Experimental animal models have confirmed the occurrence of demyelination after rapid sodium correction. In dogs and rats, demyelination follows rapid correction of sustained, vasopressin-induced hyponatremia with hypertonic saline.

The label *osmotic myelinolysis* has been suggested in preference to *central pontine myelinolysis* because of the well-recognized occurrence of extrapontine myelinolysis. This myelinolysis occurs in areas of the brain characterized by an extensive admixture and apposition of gray and white matter. Although the pathogenesis of osmotic myelinolysis remains undefined, the topography of oligodendrocytes may play a role. Oligodendrocytes in these vulnerable areas are predominantly located within adjacent gray matter rather than within the white matter bundles (Fig. 17-2). Because gray matter is much more vascular than white matter, oligodendrocytes in this location may be more vulnerable to serum osmotic shifts.

A judicious approach to the correction of chronic hyponatremia is urged, especially in cases where the sodium has been chronically depressed. There is no justification for using hypertonic saline to treat asymptomatic hyponatremia, or to rapidly correct hyponatremia to levels above 120 to 125 mEq/L in significantly symptomatic hyponatremia. The rapid reinduction of hyponatremia has shown unclear benefit in animals and humans; therefore, it should not be employed routinely to prevent or treat osmotic demyelination syndrome. Corticosteroids, *myo*-inositol, immunoglobulin, and thyrotrophin-releasing hormone have all been suggested as possible treatments of or preventive measures for the syndrome, with little evidence to recommend such therapies. The lack of proven treatment for this disorder further emphasizes the need to avoid its occurrence by slow correction of hyponatremia.

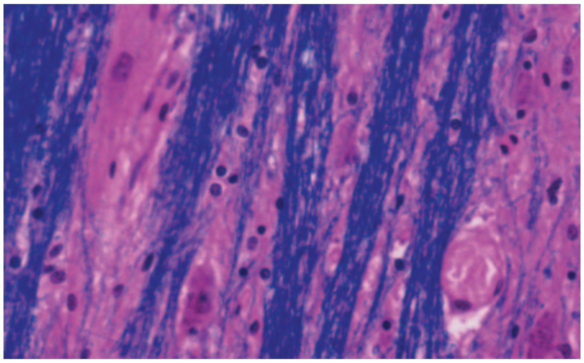

FIGURE 17-2 ■ Gray and white matter bundles in normal human pons. Note that most oligodendrocytes (*small cells with dark nuclei*) are within gray matter rather than within the white matter bundles (hematoxylin and eosin, 640 ×).

Hypernatremia

Hypernatremia is serum sodium concentrations above 160 mEq/L. It is most frequently encountered in the very young or very old. In infants, fluid loss due to gastroenteritis is a common cause. In the elderly, dehydration resulting from an inability to obtain water because of debilitation is the most frequent cause. Diabetes insipidus rarely presents with severe hypernatremia unless the patient is also denied access to water. Structural lesions (e.g., gliomas and metastatic tumors) in the hypothalamic thirst center are an uncommon cause of hypernatremia in patients with neurologic disease.

Altered mental status is a frequent manifestation of hypernatremia and ranges from lethargy to coma. Pathologic studies suggest that osmotic forces present during the development of hypernatremia, particularly when acute, may produce shrinkage of brain parenchyma. This may result in parenchymal hemorrhages or tearing of bridging veins, producing subdural hematomas or subarachnoid hemorrhage. For example, Fig. 17-3 shows a patient with acute hypernatremia before (*A*, *B*) and after treatment (*C*, *D*).[9] The patient was a 73-year-old man who presented with altered mental status, vomiting and tremor 12 hours after ingesting soy sauce in a suicide attempt. Serum sodium was 188 mEq/L and serum osmolarity was 314 mOsm/kg H_2O. MRI images (T1 left and T2 right) showed brain shrinkage and subdural fluid collections bilaterally. After sodium was corrected, imaging showed that the brain volume had been restored.

An initial mortality rate of 20 percent and an incidence of permanent brain damage of more than 33 percent have been noted in children with severe hypernatremia. Seizures may occur in the setting of hypernatremia and paradoxically may be more frequent during rehydration. These hypernatremic seizures may be related to either focal hemorrhages that occur during the development of hypernatremia or cerebral edema that may develop during rehydration. Rigidity, tremor, myoclonus, asterixis, and chorea have also been associated with hypernatremia. Transient thalamic signal changes on MRI have been seen with severe hypernatremia. Neuromuscular manifestations of hypernatremia are much less frequent. Rhabdomyolysis and episodic muscle weakness have been reported. Treatment of symptomatic hypernatremia typically involves administration of hypotonic fluids

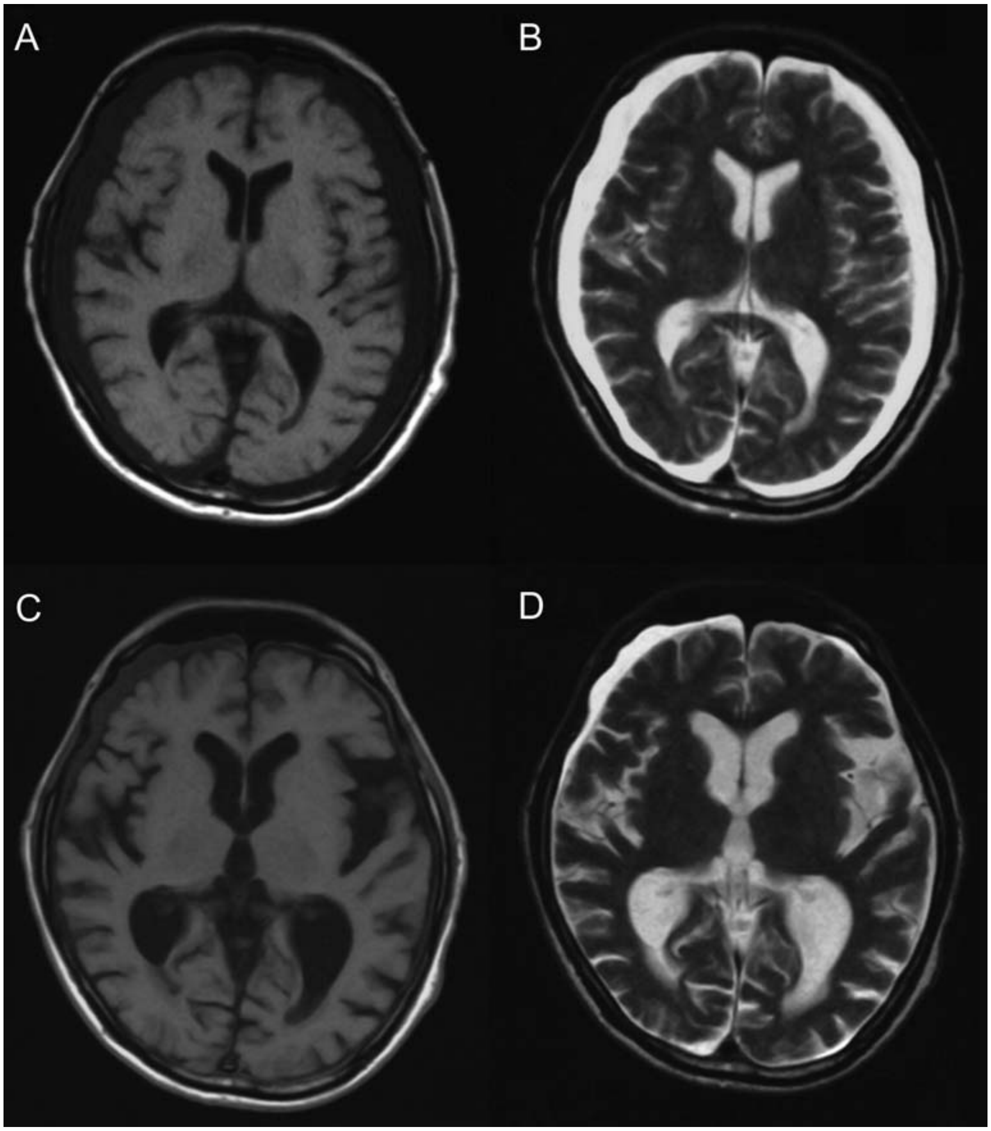

FIGURE 17-3 ■ MRI of patient with acute hypernatremia before (*A*, *B*) and after treatment (*C*, *D*). Note T1-weighted image on left shows brain shrinkage and T2-weighted image shows bilateral subdural collection. Brain volume is restored on MRI after 3 weeks. (From Machino T, Yoshizawa T: Brain shrinkage due to acute hypernatremia. Neurology 67:880, 2006, with permission.)

to correct the free water deficit, using caution to avoid rapid correction.

POTASSIUM

In contrast to sodium, the neurologic manifestations of potassium disturbance rarely involve the CNS. About 98 percent of total body potassium is located intracellularly, and 60 percent of intracellular potassium is within muscle. This distribution may, in part, account for the predominance of muscle symptoms associated with either hypokalemia or hyperkalemia.

Hypokalemia

Hypokalemia is defined as a serum potassium level of less than 3.6 mEq/L. It is the most frequent electrolyte disorder encountered in clinical practice and is produced by a variety of mechanisms, including inadequate potassium intake or excessive renal or gastrointestinal potassium loss. Neurologic symptoms of hypokalemia are typically muscular. Serum potassium concentrations of 3.0 to 3.5 mEq/L may be associated with mild muscle weakness, myalgia, and ease of fatigue. Serum potassium concentrations of 2.5 to 3.0 mEq/L are associated with the development of clinically significant muscle weakness, particularly of the proximal limb muscles, and muscle cramps. The cranial musculature is characteristically spared in hypokalemia-induced muscle weakness. When the serum potassium level falls below 2.5 mEq/L, and usually below 2.0 mEq/L, structural muscle damage, including rhabdomyolysis and myoglobinuria, may occur.

Tetany occurs in some patients with hypokalemia, particularly when associated with alkalosis. Hypokalemia may mask the tetany of hypocalcemia. Paradoxically, tetany may occur during the treatment of hypokalemia in patients who are also hypocalcemic.

Cerebral symptoms in hypokalemia are distinctly unusual. Reference to symptoms such as lethargy, apathy, drowsiness, confusion, irritability, delirium, and coma in hypokalemia are rare and suggest that an associated acid–base disturbance or other electrolyte abnormality may have been responsible for these encephalopathic symptoms. Brain concussion has been shown to lead to a mild transient hypokalemia.

Hyperkalemia

Hyperkalemia is defined as a serum potassium level exceeding 5.2 mEq/L. The cardiac toxicity of hyperkalemia essentially precludes the appearance of significant neurologic manifestations. Most patients develop serious cardiac abnormalities, such as ventricular fibrillation or asystole, before the appearance of neurologic symptoms.

The most frequent neurologic manifestation of hyperkalemia is the development of mild muscle weakness, which occurs most often in the setting of chronic adrenal insufficiency. Profound muscle weakness with hyperkalemia is reported only rarely. Chronic potassium homeostasis is dependent on renal mechanisms. Acute potassium regulation is dependent on extrarenal hormonal mechanisms primarily involving insulin, aldosterone, and epinephrine. Clinically important etiologies of hyperkalemia include renal failure, adrenal insufficiency (Addison disease), and acidosis with or without insulin deficiency. Cerebral symptoms due to hyperkalemia must be uncommon, since they do not occur in hyperkalemic periodic paralysis. The cerebral symptoms (nervousness and lethargy) that frequently occur in Addison disease are more likely related to the associated hyponatremia or acidosis than the elevated potassium.

CALCIUM

Plasma calcium stabilizes excitable membranes in muscle and nervous tissue. Disorders of calcium would therefore be expected to produce neurologic manifestations. The coordinated interactions of parathyroid hormone, cholecalciferol, and probably calcitonin regulate plasma calcium concentration. The main sources of calcium are intestinal calcium absorption, renal calcium reabsorption, and bone resorption.

Hypocalcemia

Hypocalcemia is defined as total serum calcium of less than 8.8 mg/dL or serum ionized calcium less than 4.7 mg/dL. It is relatively rare except in neonates and individuals with renal failure. Severe acute hypocalcemia is most frequently iatrogenic, following thyroid or parathyroid surgery. Hypocalcemia is also a common complication of acute pancreatitis and is frequent in patients in the intensive care unit with a variety of conditions. The neurologic manifestations of hypoparathyroidism resulting from primary, secondary, or pseudohypoparathyroidism (parathyroid hormone-resistant syndromes) largely reflect hypocalcemia.

The most common CNS manifestations of hypocalcemia are altered mental status and seizures (which may be focal or generalized). Altered mental status symptoms include irritability, anxiety, agitation, confusion, delirium, delusions, hallucinations, psychosis, depression, mental dullness, mental retardation, and dementia. Chorea and parkinsonism are seen with increased frequency in patients with chronic hypocalcemia. Although a causal relationship has not been established, the regularity with which calcification of the basal ganglia is seen in patients with chronic hypoparathyroidism seems more than coincidental, and some patients have quite prominent associated movement disorders (discussed in Chapter 58).[10] Less frequent CNS manifestations of hypoparathyroidism are pseudotumor cerebri and myelopathy due to vertebral lamina overgrowth.

Tetany is the most frequently recognized symptom of hypocalcemia referable to the peripheral nervous system. Tetany originates in the peripheral nerve axon and is due to spontaneous, irregular, repetitive nerve action potentials. When the ionized calcium concentration reaches a low enough level, the peripheral nerve membrane may spontaneously discharge at the normal resting membrane potential. Latent tetany may be unmasked clinically by hyperventilation or temporary local ischemia by an inflated blood pressure cuff (Trousseau test). The first symptom of tetany is tingling that initially occurs periorally and distally in the limbs and then spreads proximally. This is followed by a feeling of muscle spasm that has an initial distribution similar to that of the early sensory complaints and becomes increasingly severe as it spreads proximally. Finally, muscles may go into tonic spasms, commencing distally (carpopedal spasm). Laryngeal stridor may ultimately develop. Opisthotonos may occur if spasms involve the trunk.

Elevated serum creatine kinase levels have been reported in patients with hypoparathyroidism, although clinical and morphologic evidence of myopathy has been scant. Hypoparathyroidism has been associated with the mitochondrial disorder Kearns–Sayre syndrome as well as with muscle phosphorylase deficiency (perhaps related to failure of calcium to activate phosphorylase kinase).

Hypercalcemia

Hypercalcemia is defined as serum calcium levels exceeding 10.5 mg/dL. Malignant neoplasms and hyperparathyroidism account for 70 to 80 percent of cases of hypercalcemia. The neoplasms most frequently associated with hypercalcemia are breast cancer, lung cancer, and multiple myeloma. Although most instances of hypercalcemia in the setting of malignancy are due to osteolytic skeletal metastases, some carcinomas, particularly of the lung, are associated with hypercalcemia due to elevated levels of parathyroid hormone. Single adenomas of the parathyroid gland account for 75 percent of cases of primary hyperparathyroidism. Because patients with malignant neoplasms often have several mechanisms for neurologic injury, the incidence of neurologic manifestations in hyperparathyroidism (which is at least 40%) represents a reasonable incidence of the neurologic disorders associated with hypercalcemia.

Alterations in mental status are common in hypercalcemia, particularly with serum calcium concentrations of more than 14 mg/dL. Symptoms consist of progressive lethargy, confusion, and ultimately coma. These reversible symptoms are directly related to the degree of hypercalcemia and require immediate therapy. Headache, elevated cerebrospinal fluid protein, and, rarely, convulsions also occur in patients with hypercalcemia. Hyperparathyroidism has also been associated rarely with other CNS disturbances including ataxia, internuclear ophthalmoplegia, corticospinal tract dysfunction, dysarthria, and dysphagia. Hypercalcemia has been associated with apnea in children as well as with the posterior reversible encephalopathy syndrome, a radiographic diagnosis due to many etiologies that can present with seizures, altered mental status, or focal neurologic deficits.[11]

Hypercalcemia produces reduced neuromuscular excitability and may cause muscle weakness. Easy fatigability and muscle weakness are more common in hyperparathyroidism than in other hypercalcemic conditions. The clinical features of hyperparathyroid myopathy include proximal, though seldom disabling, muscle weakness and wasting with preserved or even brisk reflexes and mild nonspecific myopathic features on electromyography and muscle biopsy, as discussed in Chapter 60. The pathogenesis of hyperparathyroid myopathy remains undefined, although hypercalcemia, vitamin D deficiency, chronic phosphate deficiency, or neuropathic influences may play a role. Hyperparathyroid myopathy is similar to the vitamin D deficiency myopathy that can occur with uremia, phenytoin therapy, and osteomalacia. Neuropathy is not a common feature of hypercalcemia, but carpal tunnel syndrome has occasionally been associated with hyperparathyroidism.

MAGNESIUM

Less than 2 percent of total body magnesium is located within the extracellular fluid compartment. Although magnesium has an intracellular–extracellular distribution similar to that of potassium, most of the intracellular magnesium is bound and not exchangeable with the extracellular fluid. Intracellular free magnesium is rigidly regulated despite wide variations in extracellular magnesium concentrations. The teleologic basis for this rigid regulation is the critical role of magnesium in intracellular metabolism. Magnesium is required for activation of a wide range of intracellular enzymes. Additionally, extracellular magnesium exerts significant effects on synaptic transmission in the central and peripheral nervous system.

Hypomagnesemia

Hypomagnesemia is defined as serum magnesium concentration less than 1.6 mg/dL, although signs and symptoms do not typically arise until levels are less than 1.2 mg/dL. Because magnesium is predominantly an intracellular electrolyte, the finding of hypomagnesemia does not always accurately reflect magnesium depletion. Important mechanisms of hypomagnesemia and magnesium depletion include decreased intake (as in starvation), decreased intestinal absorption (as in malabsorption syndromes such as nontropical sprue), and increased renal loss (as with diuretic usage, chronic alcoholism, diabetic acidosis, and renal tubular acidosis).

The neurologic manifestations of hypomagnesemia are essentially hyperirritability with agitation, confusion, seizures, tremor, myoclonus, hyperreflexia, Chvostek sign, and tetany. Occasionally, even focal neurologic signs may be seen in patients with hypomagnesemia. When convulsions occur in patients with hypomagnesemia, parenteral administration of magnesium salts is required. However, renal function should be assessed before parenteral magnesium is administered as those with renal failure may not be able to excrete magnesium adequately. When magnesium is given, it should be given by slow intravenous bolus, and calcium gluconate should be available to counteract transient hypermagnesemia, which may rarely cause apnea as a result of respiratory muscle paralysis.

Hypomagnesemia and hypocalcemia need to be considered together in diagnosis and management. The neurologic manifestations of hypomagnesemia are similar to those of hypocalcemia, which is not surprising, since hypocalcemia often accompanies hypomagnesemia. The hypocalcemia or hypomagnesemia is produced or exaggerated in some instances by a hypomagnesemia-induced decrease in parathyroid hormone or end-organ resistance to the action of parathyroid hormone. This leads to an important therapeutic point—it is necessary to evaluate magnesium in a hypocalcemic patient who fails to respond to calcium supplementation. Conversely, in magnesium-deficient patients who are normocalcemic but have symptoms suggestive of hypocalcemia, calcium may still be responsible for the symptoms. Normocalcemic hypomagnesemic patients may have decreased serum ionized calcium concentrations.

Hypomagnesemia develops frequently with cisplatin use. In that setting, only patients who are also hypocalcemic develop tetany with carpopedal spasm. Muscle weakness develops in some patients with hypomagnesemia, although co-existent hypokalemia or hypophosphatemia may contribute. Chronic hypomagnesemia has been associated with a cardioskeletal mitochondrial myopathy.[12]

Hypermagnesemia

Hypermagnesemia is defined by a serum level exceeding 2.3 mg/dL (1.9 mEq/L). Symptomatic hypermagnesemia occurs rarely in the setting of excessive magnesium intake in conjunction with impaired renal function. Unsuspected symptomatic hypermagnesemia may occur more frequently in the elderly.

The predominant neurologic manifestation of severe hypermagnesemia is muscular weakness or paralysis. Untreated, this weakness, which can involve respiratory muscles, may result in respiratory insufficiency with subsequent hypoxia, hypercapnia, coma, and ultimately death. The flaccid muscle weakness of hypermagnesemia is due to a blockade of neuromuscular transmission, which may not resolve until magnesium levels return to normal through renal excretion or with the aid of hemodialysis. In general, the neurologic manifestations of hypermagnesemia are characterized by nervous system depression. Loss of deep tendon reflexes is an early sign of hypermagnesemia and occurs at serum magnesium concentrations of 5 to 6 mEq/L. This loss of reflexes may be utilized in obstetrics to titrate magnesium sulfate infusions used in the treatment of pre-eclampsia. At serum magnesium concentrations of 8 to 10 mEq/L, CNS depression is said to occur, with lethargy and confusion being the most common reported neurologic manifestations. However, in human subjects in whom the serum magnesium concentration was increased to 15 mEq/L, no CNS depression occurred, although there was slowing of the electroencephalogram. This leads to the conclusion that clinical CNS effects of hypermagnesemia are likely rare.

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SECTION

4

Endocrine Disorders

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CHAPTER

18

Thyroid Disease and the Nervous System

NICK VERBER ■ PAMELA J. SHAW

NEUROLOGIC COMPLICATIONS OF HYPOTHYROIDISM

- Neurologic Features of Congenital Hypothyroidism
- Encephalopathy, Coma, and Seizures
- Mental Changes
- Disorders of Sleep
- Cerebellar Ataxia
- Cranial Nerve Disorders
- Hypothyroid Myopathy
  - *Clinical Features*
  - *Investigations*
  - *Pathology*
  - *Pathophysiology*
  - *Treatment and Prognosis*
- Peripheral Neuropathy
  - *Entrapment Neuropathy*
  - *Diffuse Peripheral Neuropathy*
- Miscellaneous Associated Conditions
  - *Myasthenia Gravis*
  - *Giant Cell Arteritis and Polymyalgia Rheumatica*
  - *Hypothyroidism and Anticonvulsant Therapy*

NEUROLOGIC COMPLICATIONS OF HYPERTHYROIDISM AND GRAVES DISEASE

- Hyperthyroid Myopathy
  - *Clinical Features*
  - *Physiologic and Biochemical Changes in Skeletal Muscle*
  - *Pathology*
  - *Treatment and Prognosis*
- Periodic Paralysis
  - *Clinical Features*
  - *Physiology and Pathophysiology*
  - *Treatment*
- Myasthenia Gravis
- Peripheral Neuropathy
- Corticospinal Tract Dysfunction
- Movement Disorders
  - *Chorea*
  - *Tremor*
  - *Other Movement Disorders*
- Thyroid-Associated Ophthalmopathy
  - *Clinical Features*
  - *Diagnostic Tools*
  - *Pathogenesis*
  - *Treatment*
- Encephalopathy
- Seizures
- Mental and Psychiatric Disorders
- Stroke
- Hashimoto Encephalopathy
  - *Clinical Features*
  - *Pathophysiology*
  - *Diagnosis*
  - *Treatment*

MISCELLANEOUS ASSOCIATIONS BETWEEN NEUROLOGIC DISORDERS AND THYROID DYSFUNCTION

- Endocrine Dysfunction in Long-Term Survivors of Primary Brain Tumors
- Multiple Sclerosis and Thyroid Disease
- Recurrent Laryngeal Nerve Palsy

Disorders of the thyroid gland are common and are frequently accompanied by neurologic complications. Prevalence estimations have suggested that 1 to 2 percent of general medical, geriatric, and psychiatric inpatients have some form of thyroid disease. Neurologists should be aware of the common and the more unusual neurologic complications of thyroid disease, since they may be the presenting feature of the thyroid disorder and because they are usually readily corrected with appropriate treatment.

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NEUROLOGIC COMPLICATIONS OF HYPOTHYROIDISM

Hypothyroidism is a common disorder, with data from the National Health and Nutrition Examination Survey indicating that 1 in 300 persons in the United States has hypothyroidism. The commonest causes of hypothyroidism are autoimmune destruction, thyroidectomy, and radioiodine ablation of the gland. Fewer than 10 percent of cases of hypothyroidism are secondary to pituitary or hypothalamic disease.

Neurologic complications are common in patients with hypothyroidism, and all levels of the nervous system may be involved. The neurologic complications of hypothyroidism may be grouped into the following categories: (1) congenital hypothyroidism; (2) encephalopathy that may result in coma or a seizure disorder; (3) psychologic changes; (4) sleep disorders; (5) cerebellar ataxia; (6) cranial nerve lesions; (7) myopathy; (8) peripheral nerve disorders; and (9) miscellaneous conditions.

Neurologic Features of Congenital Hypothyroidism

Congenital hypothyroidism (CH), previously called cretinism, is the commonest treatable cause of neonatal encephalopathy, with data from neonatal screening programs revealing an incidence of 1:3,000 to 1:4,000. It occurs secondary to dysgenesis of the thyroid gland or to severe maternal deficiency of dietary iodine. Neurologic complications include developmental delay, pyramidal signs in a proximal distribution, and extrapyramidal signs. Many patients have a characteristic gait, reflecting dysfunction of both the pyramidal and the extrapyramidal motor systems, in combination with laxity and deformity of the joints. Other common clinical features include strabismus, deafness, ataxia, and primitive reflexes. Imaging of the brain shows basal ganglia calcification in one-third of patients. In addition, evidence suggests that CH leads to reduced hippocampal volume, even when treated, and psychometric testing reveals that patients score below age-matched controls in verbal memory. Similarly, reduced IQ scores have also been reported in children with CH. Learning impairment and changes in hippocampal CA1 pyramidal cell excitability have been reported in hypothyroid mice.

Adult patients with CH typically manifest physical signs of spasticity affecting the trunk and proximal limb-girdle musculature, with relative sparing of the distal extremities. Magnetic resonance imaging (MRI) of the brain has shown abnormalities in the globus pallidus and substantia nigra, with increased signal on T1-weighted images and hypointensity on T2-weighted images, and only a modest degree of cerebral atrophy. Overall however, neuroradiologic findings seem to be similar in children with CH when compared to healthy controls. It has been suggested that the main insult to the central nervous system (CNS) may involve processes such as dendritic arborization and synaptogenesis, which are not evident on MRI.

In the developing brain, thyroid hormone has important effects on the regulation of neurofilament gene expression and on several genes encoding mitochondrial proteins. Thyroid hormone also regulates the timing of appearance and regional distribution of laminin, an extracellular matrix protein that provides key guidance signals to migrating neurons within the CNS. Disruption in the expression of laminin may play a role in the derangement of neuronal migration observed in the brain of patients with CH.

A detailed consideration of the inborn errors of thyroid gland development and thyroid hormone synthesis responsible for permanent CH is beyond the scope of this chapter, but recent reviews on the topic provide additional details.[1] Primary CH is due to abnormal development of the thyroid gland in 85 percent of instances. A group of patients with CH poorly responsive to treatment and featuring additional signs of choreoathetosis, muscular hypotonia, and pulmonary problems were found to have mutations to thyroid transcription factor 1. Mutations to genes coding proteins required for thyroid hormone synthesis cause 10 to 15 percent of permanent primary CH; thyroid peroxidase is the protein most commonly affected. Furthermore, mutations in a transmembrane thyroid hormone transporter, MCT-8, result in abnormal levels of circulating iodothyronines as well as global developmental delay, central hypotonia, spastic quadriplegia, dystonic movements, rotatory nystagmus, and impaired gaze and hearing in affected males. Heterozygous females have a milder thyroid phenotype and no neurologic abnormalities.

Encephalopathy, Coma, and Seizures

Slowness, impairment of attention and concentration, somnolence, and lethargy are common symptoms in hypothyroidism. Occasionally, a life-threatening encephalopathy termed "myxedema coma" develops in patients with chronic, untreated hypothyroidism. A high index of suspicion is required to diagnose myxedema coma, particularly in the elderly, in whom features of hypothyroidism may be difficult to distinguish from depression or dementia.

In the compensated hypothyroid state, physiologic adaptations include a shift of the vascular pool away from the periphery to the central core to sustain normal body temperature. In chronic hypothyroidism, these adaptations tend to produce a degree of diastolic hypertension as well as a decrease in blood volume of up to 20 percent. Many organ systems and metabolic pathways are profoundly altered by chronic deficiency of thyroid hormone. Alterations in myocardial biochemistry produce impairment of cardiac contractility; the ventilatory response to hypercapnia is abnormal; hyponatremia may result from a reduction in free water clearance; and suppression of bone marrow function may result in normochromic normocytic anemia and an impaired white blood cell response to infection. Reduction in insulin clearance and decreased gluconeogenesis may produce a tendency to hypoglycemia, and patients are predisposed to toxic drug effects owing to reduced plasma clearance of all drugs. The corticosteroid response to stress is also likely to be impaired, even when basal serum cortisol levels are normal.

The majority of patients who develop myxedema coma are elderly and have a history suggestive of gradual deterioration. Three key clinical features are universally present in myxedema coma: depression of consciousness, a precipitating illness or event, and defective temperature control. Common precipitating factors include infection, trauma, stroke, hypothermia, hypoglycemia, carbon dioxide narcosis, and administration of certain drugs that have a CNS depressant effect. The body temperature is subnormal in many cases, but relative hypothermia may also occur, with the patient having an inappropriately normal temperature in the presence of sepsis. Most patients have clinical signs in keeping with long-standing hypothyroidism. Seizures occur in approximately 20 percent of cases; focal neurologic signs are not usually observed unless there has been a concomitant cerebrovascular event.

The pathophysiology is not fully understood but centers on the effects of low intracellular triiodothyronine (T3), particularly on the heart, which leads to decreased inotropism and chronotropism. Laboratory investigations are often abnormal but seldom show diagnostic abnormalities. In critically ill patients, it may be difficult to distinguish between severe hypothyroidism and the sick euthyroid syndrome, and it may be necessary to measure levels of free circulating thyroid hormone. The electrocardiogram typically shows sinus bradycardia, with low voltage and prolongation of the QT interval. Chest radiography may reveal a pleural or pericardial effusion. Hyponatremia may be present, and the serum cholesterol level is sometimes elevated. Serum creatine kinase (CK) and lactate dehydrogenase levels are often raised. Lumbar puncture may reveal an elevated opening pressure, and the cerebrospinal fluid (CSF) protein concentration is often raised. The electroencephalogram (EEG) is commonly abnormal; in keeping with a metabolically induced encephalopathy, the frequency of the posterior dominant rhythm decreases, often into the theta range, and triphasic waves may be present.

The key to the successful treatment of myxedema coma is early recognition and the rapid institution of appropriate therapeutic measures, usually in the intensive care unit (ICU). Hypothyroid coma has a high mortality rate, and treatment should not be delayed for confirmatory laboratory data. Besides the use of intravenous thyroxine, it should include broad-spectrum antibiotics to cover any underlying infection and stress doses of glucocorticoids until specific laboratory results become available. Patients may not mount an appropriate leukocyte response or fever even in the presence of severe infection. The main principles of management also include correction of electrolyte and blood sugar abnormalities, passive rewarming, control of seizures, and respiratory and circulatory support. Different specific treatment regimens are advocated, with some authors preferring thyroxine (T4) monotherapy at a loading dose of 200 to 300 μg intravenously followed by 100 μg intravenously for maintenance. When stable, oral replacement at a dose of 1.6 μg/kg can be used with dose adjustment guided by thyroid-stimulating hormone (TSH) and free T4 levels.[2]

Early recognition and improved ICU care have improved outcomes, but mortality remains at around 20 percent[2]; factors associated with poor outcome include hypotension and bradycardia at presentation, sepsis, reduced Glasgow Coma Scale score, the need for mechanical ventilation, and hypothermia unresponsive to treatment.

Neuropathologic studies of patients with myxedema coma have been few and usually have shown only the presence of cerebral edema with or without diffuse neuronal changes.

There is a relatively high incidence of seizures in hypothyroidism, occurring in up to 20 percent of untreated patients. Drop attacks (sudden repeated falls without warning symptoms and without loss of consciousness) also occur and resolve with therapy. Patients with severe hypothyroidism may present with convulsive or nonconvulsive status epilepticus. Clinicians should be alert to the possibility of underlying hypothyroidism when the recovery time of the patient following a seizure is unusually prolonged.

Mental Changes

Hypothyroidism may be associated with mood disorders, in particular, depression.[3] Treatment of the hypothyroidism usually resolves the affective problem, although the response of individuals to treatment may be modulated by common polymorphisms of thyroid hormone transporters and deiodinases.[3] The colorful term *myxedema madness* has been used to describe the florid mental-state changes that may occur in hypothyroid patients, including irritability, paranoia, hallucinations, delirium, and psychosis. These symptoms are typically reversible but often take longer than physical symptoms to resolve; in some cases a degree of cognitive impairment may persist, particularly if treatment is delayed, perhaps due to irreversible damage secondary to chronic metabolic changes.

An increased incidence of hypothyroidism has been noted in patients with various major psychiatric illnesses. For example, there is an association between hypothyroidism and bipolar affective disorder, particularly in patients with a "rapid cycling" form of the illness, and up to 50 percent of these patients have positive antithyroid antibody titers. Clinical and subclinical hypothyroidism in depression and bipolar disorder may adversely affect or delay the response to treatment. Many patients with depression, even when viewed as chemically euthyroid, have alterations in their thyroid function, including slight elevation of the serum thyroxine, blunting of the TSH response to thyrotropin-releasing hormone stimulation, and detectable titers of antithyroid antibodies. These changes are generally reversed following alleviation of the depression. It has also been recognized that depressed patients with hypothyroidism may manifest different symptoms than patients with low mood and no concurrent hypothyroidism. Generally speaking, hypothyroidism is a reversible cause of cognitive impairment, most commonly manifesting as psychomotor slowing, memory impairment, visuospatial problems, and reduced constructional dexterity.

More subtle neuropsychologic abnormalities have also been documented in hypothyroid patients and may include impairment of learning, word fluency, and some aspects of attention, visual scanning, and motor speed. Treatment of the hypothyroidism may result in some cognitive improvement. Mood and neuropsychologic function may improve more satisfactorily in hypothyroid patients treated with a combination of thyroxine plus triiodothyronine, rather than thyroxine alone.

Disorders of Sleep

Both obstructive and central sleep apnea may occur in patients with hypothyroidism. Obstructive sleep apnea (OSA) appears to be far more common, with estimates that the prevalence is over 50 percent in patients with hypothyroidism, while the prevalence of hypothyroidism in all OSA patients is less than 3 percent. The combination of hypothyroidism and OSA appears to increase the risk of cognitive impairment. Factors contributing to the development of OSA include narrowing of the upper airway due to deposition of mucopolysaccharides and extravasation of protein into the tissues of the tongue and nasopharynx, as well as hypertrophy of the genioglossus. Centrally, there appears to be reduced chemosensitivity to hypercapnia.

Thyroid hormone replacement therapy usually results in improvement in ventilatory drive following normalization of TSH. Improvement in airway dimensions may require a longer period of euthyroidism (up to 12 months), and only at this stage will nocturnal snoring decrease. In some patients, additional measures such as nasal continuous positive airway pressure may be required.

Cerebellar Ataxia

Reference to unsteadiness of gait may be found in the earliest clinical descriptions of hypothyroidism. In a recent review of the literature, it was found that all patients develop significant broad-based gait, and other typical clinical features include, in decreasing frequency, incoordination of the limbs, cerebellar dysarthria, nystagmus, and vertigo.[4] Rapid and complete or almost complete resolution of the cerebellar features usually occurs following achievement of euthyroidism.

The pathophysiologic basis of cerebellar dysfunction in hypothyroidism remains unknown. The rapid resolution of the ataxia with thyroid replacement therapy in most patients suggests a reversible metabolic factor. However there may be an immune-mediated mechanism of cerebellar degeneration in those patients that have been noted to be ataxic despite being euthyroid. For this latter group, immunosuppression may be a therapeutic option. Pathologic reports are few, but depletion of Purkinje cells may occur. Changes on imaging are rare, but MRI may demonstrate atrophy of the vermis and cerebellar hemispheres.[4]

Cranial Nerve Disorders

Primary thyroid failure may be associated with pituitary enlargement resulting from hyperplasia due to lack of negative feedback from circulating thyroid hormones. Pituitary enlargement, as determined on MRI, has been found in 70 percent of patients with primary hypothyroidism, and a reduction in pituitary size following treatment occurs in the majority. Visual evoked potentials may be abnormal in hypothyroid patients, but severe visual field loss and blindness are rare. The association between pituitary gland enlargement and primary hypothyroidism should be kept in mind when pituitary hyperplasia is detected on neuroimaging, so that unnecessary invasive interventions are avoided.

Some patients with hypothyroidism develop pseudotumor cerebri (idiopathic intracranial hypertension) resulting in headache and papilledema following the initiation of thyroxine replacement therapy. An atypical facial pain syndrome may also occur.

Hearing impairment and tinnitus commonly occur in patients with hypothyroidism. Estimations of reduced auditory acuity based on pure-tone audiometry vary, but it is likely that over half of patients suffer hearing impairment that may originate from the cochlea, central auditory pathways, or the retrocochlear region. The hearing loss associated with hypothyroidism is thought to be sensorineural in nature and may improve when the hypothyroidism is treated.

Dysphonia in patients with hypothyroidism appears to arise from local myxedematous changes in the larynx rather than from cranial nerve dysfunction.

Hypothyroid Myopathy

CLINICAL FEATURES

Muscle involvement is common in clinical and subclinical hypothyroidism, with more than 60 percent of patients reported to have an elevated serum CK level.[5] The level of increase correlates with the severity of hypothyroidism and corrects when thyroid function normalizes with treatment. Symptomatic muscle disease is less common. Clinical evidence of hypothyroid myopathy occurs in 30 to 80 percent of patients. A study of clinical and electrophysiologic features prior to commencement of thyroxine therapy revealed that 45 percent of patients with hypothyroidism had decreased or absent deep tendon reflexes, 30 percent had clinical muscle weakness, 15 percent had neuropathy, and 8 percent had evidence of myopathy on electromyography (EMG).[5]

The major clinical features of hypothyroid myopathy include weakness, cramps, aching or painful muscles, sluggish movements and reflexes, and myoedema (mounding of the muscle on direct percussion). There may be a discernible increase in muscle bulk that is most obvious in the tongue, arms, and legs. The degree of weakness is usually relatively mild and tends to involve the pelvic- and shoulder-girdle muscles. The gait tends to be slow and clumsy. Occasionally, patients have been described with more severe myopathic symptoms, including the development of rhabdomyolysis and renal failure or, very rarely, respiratory insufficiency, which may respond to hormone replacement. Muscle pain, particularly during and after exertion, is a prominent feature, and hypothyroidism should be considered in patients presenting with musculoskeletal pains of uncertain cause.

Muscle pain, stiffness, cramps, and delayed relaxation of the tendon reflexes in adult hypothyroidism are sometimes referred to as Hoffmann syndrome.

Kocher–Debré–Sémélaigne syndrome is the unusual association of muscle hypertrophy with childhood hypothyroidism. The patient may have the typical clinical features of CH, with the added feature of generalized muscular hypertrophy so that the child has an athletic, almost Herculean appearance.

A delay in the relaxation of muscle (pseudomyotonia) is commonly observed during assessment of the tendon reflexes in hypothyroid patients. All phases of the tendon reflex are delayed, although slowing of the relaxation phase is most apparent clinically. Pseudomyotonia differs from true myotonia in that there is reduction in the speed of both the contraction and relaxation phases, and this slowness is not increased after rest or relieved by repeated muscle contractions. EMG does not show the characteristic "dive-bomber" effect seen in true myotonia; in the pseudomyotonia of hypothyroidism, there is a continuous burst of action potentials that begins and terminates abruptly, with firing at a constant rate. Percussion of the muscle commonly causes a slow prolonged mounding effect (myoedema). This event, unlike myotonia, is electrically silent and has been attributed to derangement of intracellular calcium homeostasis.

The differential diagnosis of hypothyroid myopathy includes other causes of painful stiff muscles, such as polymyalgia rheumatica and polymyositis. Attention has been directed to the frequency of neuromuscular symptoms in patients with subclinical hypothyroidism, and the suggestion has been made that such patients should be treated early, not only to prevent progression to frank hypothyroidism, but also to improve neuromuscular dysfunction.

INVESTIGATIONS

The majority of patients with hypothyroidism have an elevated serum CK level, even when the myopathic features are not clinically obvious. In symptomatic patients, the serum CK level may rise to more than 10 times the upper limit of normal.[5] Due to the patchy nature of the myopathy, neurophysiologic assessment may show no significant abnormalities. However, up to one-third of patients with hypothyroidism may have "myopathic" short-duration, low-amplitude, polyphasic motor unit potentials on EMG.

PATHOLOGY

In many cases of hypothyroidism, pathologic changes in muscle are subtle and nonspecific. Light microscopy may reveal increased central nuclear counts, type I fiber predominance, or type II fiber atrophy; common abnormalities on electron microscopy include the accumulation of glycogen and lipids, abnormal and increased numbers of mitochondria in perinuclear and subsarcolemmal regions, dilated sarcoplasmic reticulum, and focal myofibrillar degeneration.[5] There may be vacuolation in many large fibers, and crescents of material containing acid mucopolysaccharides may be found beneath the sarcolemmal sheath. Often these changes resolve with thyroxine replacement therapy.

PATHOPHYSIOLOGY

Thyroid hormone is intimately linked to carbohydrate metabolism, mitochondrial function, and possibly to the function of the sarcoplasmic reticulum and intrinsic contractile properties of muscle. However, these structure–function relationships are still incompletely understood, although it is assumed that underlying biochemical changes in hypothyroidism lead to prolongation of the contraction and relaxation phases of muscle activity. Magnetic resonance spectroscopy of hypothyroid muscle shows a low intracellular pH in resting muscle and delayed glycogen breakdown in exercising muscle. In addition, mitochondrial oxidative capacity is reduced in hypothyroidism.[5] Low levels of the mitochondrial transcription factor A (h-mtTFA), a proposed thyroid hormone target, occur in hypothyroid myopathy, and abnormal h-mtTFA turnover may be implicated in mitochondrial alterations in the condition. The decreased responsiveness to adrenergic stimulation and alterations in muscle carbohydrate metabolism may contribute to the impaired ischemic lactate production, weakness, exertional pain, and fatigue occurring in hypothyroidism. Hypothyroidism is associated with changes in myosin, lactate dehydrogenase, and myofibrillar ATPase activity. These changes may underlie the observed slowing of muscle contraction and relaxation. Both protein synthesis and breakdown are reduced in hypothyroidism, resulting in net protein catabolism.

TREATMENT AND PROGNOSIS

The only effective therapy for hypothyroid myopathy is to restore the patient to the euthyroid state. Most patients respond to thyroxine therapy with complete clinical and biochemical recovery; however, some patients require prolonged therapy with thyroxine before they recover from their muscle disorder and some may never regain full function. Serum CK levels correct rapidly with thyroxine replacement therapy. Some patients may develop increased muscle pain and weakness after starting thyroxine replacement, and the short-term addition of corticosteroid therapy may be helpful if this problem arises.

Peripheral Neuropathy

Hypothyroidism may be complicated by the development of entrapment mononeuropathies or a more diffuse peripheral neuropathy.

Entrapment Neuropathy

Evidence of entrapment neuropathy is found in around 35 percent of patients with hypothyroidism. The most common mononeuropathy is carpal tunnel syndrome involving compression of the median nerve at the wrist from deposition of acid mucopolysaccharides in the nerve and surrounding tissues. Surgical decompression for the median nerve entrapment is not usually required in patients with underlying hypothyroidism, as symptoms gradually resolve once euthyroidism is achieved.

Diffuse Peripheral Neuropathy

The peripheral neuropathy of hypothyroidism is usually a relatively mild, predominantly sensory axonal peripheral neuropathy. The symptoms of peripheral neuropathy in patients with hypothyroidism may be masked by more intrusive symptoms. Perhaps for this reason, the reported incidence of peripheral neuropathy has varied widely, ranging from 15 to 60 percent. Damage to small-diameter nerve fibers also occurs, and a minority of patients may have only small-fiber involvement. In patients with a generalized large-fiber neuropathy, the severity appears to correlate with the duration of the disease rather than the degree of the biochemical disorder. Multifocal motor neuropathy, associated with elevated titers of IgM antibodies against GM1 and responsive to intravenous immunoglobulin therapy, has also been associated with Hashimoto thyroiditis.

The pathologic changes described in hypothyroid neuropathy include axonal degeneration, segmental demyelination, and deposition of mucopolysaccharides in the endoneurial interstitium and perineurial sheath. Opinions have varied as to whether axonal degeneration or demyelination is the primary pathologic process, but most reports favor a primary axonal pathology.

Miscellaneous Associated Conditions

Myasthenia Gravis

An association between hypothyroidism and myasthenia gravis has been reported, although this is less common than the association of myasthenia gravis with hyperthyroidism.[6] Myasthenic symptoms can appear before, with, or after the development of hypothyroidism, and the severity of the myasthenia may or may not improve following treatment of the hypothyroidism.

Giant Cell Arteritis and Polymyalgia Rheumatica

An association of giant cell arteritis and polymyalgia rheumatica with hypothyroidism has long been appreciated. Clinicians managing such patients should be careful not to misinterpret the musculoskeletal symptoms of hypothyroidism as an exacerbation of previously diagnosed polymyalgia rheumatica.

Hypothyroidism and Anticonvulsant Therapy

Subclinical hypothyroidism may occur in children with epilepsy treated with valproic acid or carbamazepine therapy. Rare cases of central hypothyroidism believed to be secondary to treatment with oxcarbazepine have been reported. Phenytoin may also impact thyroid function, either by inducing hypothyroidism or by worsening pre-existing hypothyroidism. Hypothyroidism also increases the risk of phenytoin toxicity.

NEUROLOGIC COMPLICATIONS OF HYPERTHYROIDISM AND GRAVES DISEASE

There are several potential underlying causes of hyperthyroidism including: (1) Graves disease; (2) excess release of stored hormone during subacute thyroiditis or following thyroid irradiation; (3) uncontrolled hormone formation in single or multinodular goiters (Plummer disease); (4) ingestion of excess thyroid hormone; (5) rare TSH-secreting pituitary tumors; and (6) drug-induced disease. Graves disease is the commonest cause of thyrotoxicosis and occurs with a female-to-male preponderance of 7:1. The neurologic complications of hyperthyroidism are diverse.

Hyperthyroid Myopathy

CLINICAL FEATURES

Muscle weakness and wasting in patients with thyrotoxicosis were observed in early classic descriptions of the condition. A degree of predominantly proximal muscle weakness probably occurs in almost every patient with hyperthyroidism. The muscle weakness may not always be sufficiently severe for the affected individual to be aware of it. Men appear to develop symptomatic myopathy more commonly than women. The thyroid overactivity can be relatively mild and of long duration, or may be present for only a few weeks before the onset of weakness. Approximately two-thirds of hyperthyroid patients may have neuromuscular complaints at the time of diagnosis of thyroid dysfunction, and marginally fewer have objective muscle weakness. In addition, myalgias and elevated serum CK levels have been reported in hyperthyroid patients after commencement of therapy, suggesting that relative hypothyroidism may also contribute to musculoskeletal complaints in previously hyperthyroid patients.

Individuals with thyrotoxic myopathy characteristically complain of difficulty with activities involving use of the shoulder- and pelvic-girdle muscles, such as climbing stairs, rising from a low chair, or performing tasks that involve raising the arms above the head. Muscle pain and stiffness are commonly associated symptoms, and occasionally patients report severe muscle cramps. Symptomatic weakness of the bulbar musculature resulting in dysphagia and dysarthria is very uncommon in hyperthyroidism and usually follows the development of limb weakness, although there are reports of isolated bulbar dysfunction (sometimes of acute onset) attributed to hyperthyroid myopathy. Bulbar symptoms in hyperthyroid patients may not be due to bulbar myopathy but may have another cause. A large goiter or thymic hyperplasia may physically compress the esophagus, leading to mechanical dysphagia, or compress the recurrent laryngeal nerve, leading to dysphonia. Involvement of the respiratory muscles occurs rarely but may necessitate ventilatory support. Muscle wasting is commonly found on examination of patients and most notably affects proximal girdle muscles such as the deltoid, supraspinatus, and quadriceps muscles. Some patients, especially males, show gluteal muscle wasting, and in some patients winging of the scapula is noticeable. The presence of tremor may create the appearance of muscle fasciculations; these disappear if the limb is relaxed. The tendon reflexes are normal or hyperactive, with shortening of the relaxation phase. Other features of thyrotoxicosis may not be obvious or may be masked, for example, if the patient is on β-blocker therapy.

These neuromuscular features may resemble the progressive muscular atrophy variant of motor neuron disease. The severity of the muscle weakness may be marked, but most patients retain the ability to walk. Acute thyrotoxic myopathy is rare and some have doubted its existence, suggesting that most of the described cases had myasthenia gravis superimposed on the hyperthyroid state. Patients present with muscle weakness progressing rapidly over a few days; weakness may be profound, bulbar muscles are often affected, and the patient may develop respiratory failure. The tendon reflexes may be reduced or absent. Some patients develop an associated encephalopathic state.

In contrast to hypothyroid myopathy, the serum CK level in hyperthyroid myopathy is usually normal or reduced, although rhabdomyolysis and elevation of the serum CK level may occur. EMG abnormalities are found in most patients with thyrotoxicosis and include the typical features of myopathy.

PHYSIOLOGIC AND BIOCHEMICAL CHANGES IN SKELETAL MUSCLE

Skeletal muscle is a major target organ of the thyroid hormones so it is not surprising that the biochemistry, electrophysiology, and even structure of skeletal muscle can be profoundly affected by an excess of thyroid hormone. A detailed examination of this literature is beyond the scope of this review, and more detailed consideration of the subject can be found elsewhere.[7]

Hyperthyroidism affects both the physiologic and the biochemical properties of skeletal muscle with a preferential effect on type I (slow) muscle fibers, shifting their characteristics toward those resembling fast muscle fibers. The speed of muscle contraction is enhanced and its duration is reduced. This effect underlies the clinical observation that the duration of muscle contraction after a deep tendon is struck with a tendon hammer is briefer than normal in the hyperthyroid state and prolonged in the hypothyroid state. The expression of isotypes of the myosin heavy chain is altered in hyperthyroidism to favor expression of MHC type IIx associated with fast-fiber characteristics, with this isoform replacing MHC type I associated with slow-fiber characteristics. These changes reverse on treatment.

The pattern of glycogen utilization and lactate production in muscle is also altered in hyperthyroidism, resulting in increased energy requirements for normal function. Thyrotoxic patients have higher concentrations of phosphocreatine at rest, and a larger magnitude of glycolysis activation during exercise, resulting in a marked decrease in pH. Additionally, in hyperthyroidism the mitochondrial transport chain is uncoupled, which promotes thermogenesis rather than energy production.

PATHOLOGY

There is no pathognomonic pathologic finding in hyperthyroid myopathy. Biopsy may be needed on occasion to exclude other pathologic processes. Microscopic examination may show no abnormality or varying degrees of fiber atrophy, fatty infiltration, and nerve terminal damage, with clubbing of the motor end-plate and swelling of terminal axons. Most patients show an increase in mitochondrial size and number in muscle fibers.

TREATMENT AND PROGNOSIS

Computed tomography (CT) and isometric strength tests suggest that muscle mass of thyrotoxic patients is reduced by approximately 20 percent and muscle strength by about 40 percent. Normal muscle mass and power can be expected to be restored 3 to 9 months following treatment. Dysphagia and dysarthria due to hyperthyroid myopathy also typically resolve after treatment.

Periodic Paralysis

Hypokalemic periodic paralysis as a complication of hyperthyroidism is relatively common in Asian populations, with a reported incidence of about 1.9 percent in those with thyrotoxicosis.[8] The disorder is rare in other ethnic groups, but the effects of globalization on population mobility mean that it is now seen more often in other parts of the world. Periodic paralysis may occur in association with hyperthyroidism of any cause, but is most commonly seen in patients with Graves disease.

CLINICAL FEATURES

Except for concomitant features of thyrotoxicosis, the clinical picture of thyrotoxic periodic paralysis (TPP) is identical to that seen in familial hypokalemic periodic paralysis (FHPP). Males are affected much more commonly than females. Affected individuals develop recurrent attacks of flaccid weakness, which may be asymmetric and affect the lower more than the upper limbs, and the proximal more than the distal muscles. The attacks may be heralded by prodromal symptoms of muscle aching, stiffness, or cramps. The weakness usually develops rapidly and varies in severity from mild weakness to total paralysis. The muscles most vigorously used before an attack tend to be most severely affected. Bulbar, ocular, and respiratory muscles tend to be spared, although there have been occasional reports of respiratory compromise. Cardiac dysrhythmias occasionally accompany the paralytic attacks. Usually, the tendon reflexes are depressed or absent during an attack, but in some patients they remain normal. Weakness usually resolves within 24 hours, but in the wake of severe attacks weakness and muscle pain may persist for several days. Patients may be able to abort impending attacks by mild exercise.

Attacks may occur with or without a triggering factor. Recognized precipitants include high carbohydrate intake, strenuous physical activity followed by a period of rest, trauma, cold exposure, infection, menses, and drugs, including amiodarone and corticosteroids.[8] A seasonal pattern of attacks has been recognized, with episodes being more common in the summer months. There is also a characteristic diurnal pattern, with attacks frequently developing during the night while patients are in bed.

The cardinal biochemical abnormality during an attack of TPP is hypokalemia resulting from an intracellular shift in potassium. Although serum potassium decreases during the attack, it may not always decline below the normal range. Urinary excretion of potassium is reduced with a low potassium–creatinine ratio. The neuromuscular symptoms resolve over a period of hours as potassium moves back to the extracellular space.

Between attacks, a long exercise test may prove a useful diagnostic aid. In this test, a pre-exercise compound muscle action potential (CMAP) is recorded from a selected muscle. The patient then performs maximal voluntary muscle contractions for 5 minutes, with relaxation for 3 to 4 seconds every 15 seconds or so to avoid muscle ischemia. The CMAP is then recorded every 2 minutes until the amplitude of the elicited potential stabilizes. The test is interpreted as positive if the decrement exceeds 40 percent.

The most consistent ultrastructural finding in muscles from patients with thyrotoxic periodic paralysis is a proliferation and focal dilatation of the sarcoplasmic reticulum and transverse tubular system, resulting in the appearance of vacuoles. These vacuoles are characteristically seen in paralyzed muscles and are less apparent between attacks.

PHYSIOLOGY AND PATHOPHYSIOLOGY

Attacks of weakness in TPP are clinically similar to those of FHPP, a channelopathy caused by inherited defects to genes encoding sodium and calcium channels in skeletal muscle. This phenotypic similarity led investigators to postulate that TPP might also be a channelopathy, albeit one that manifests only in the presence of excess thyroid hormone. It is thought that TPP patients have a genetic predisposition to the disease unmasked by independently occurring hyperthyroidism.

Gene sequencing in cohorts of largely Asian TPP patients has revealed no mutations in FHPP-causing genes or in the components of the sodium–potassium ATPase (Na^+,K^+-ATPase) pump. However, six different mutations to an inwardly rectifying potassium channel, Kir2.6, expressed strongly in skeletal muscle, were found in 33 percent of an unrelated cohort of TPP patients from the United States, Brazil, and France, as well as 25 percent of a Singaporean cohort, but none of 31 patients from Thailand.[9] The mutations discovered all have effects upon the stability of the muscle cell membrane, altering its excitability. The gene for Kir2.6 is transcriptionally regulated by thyroid hormone, and levels of the channel are increased in hyperthyroidism, explaining why it is only in this circumstance that the mutation becomes manifest. A susceptibility locus has been identified near the gene for Kir2.1, which is also highly expressed in skeletal muscle and can associate with other K^+ channels, including Kir2.6. Incorporation of Kir2.6 into the channel heterotetramer reduces the abundance of Kir2-type channels on the plasma membrane with consequences for membrane excitability.

Mutations in potassium channels appear to combine with other factors to produce the clinical phenotype. Thyroid hormones increase the activity of the Na^+,K^+-ATPase, which drives K^+ into cells; catecholamines have a similar effect. The Na^+,K^+-ATPase pump is also stimulated by insulin, hence attacks may be precipitated by carbohydrate-rich meals and exercise. In addition, testosterone appears to drive the Na^+,K^+-ATPase pump, while estrogen and progesterone reduce activity, perhaps explaining the male preponderance. Interestingly, men with TPP have higher levels of testosterone than men with a sole diagnosis of thyrotoxicosis. These effects on the Na^+,K^+-ATPase pump sum together to increase the intracellular K^+ concentration and as the efflux usually permitted by outwardly rectifying K^+ channels is reduced, a paradoxical depolarization occurs inactivating Na^+ channels. As a result, the hypokalemia seen in attacks of weakness in TPP is not due to loss of potassium, but rather to the shift of extracellular potassium into cells driven by the Na^+,K^+-ATPase pump, which has direct implications for treatment.

TREATMENT

First, emergency treatments of the attack of weakness, hypokalemia, and any complications are required. TPP patients presenting with severe weakness are treated with potassium chloride to speed recovery. Urgent assessment of cardiac and respiratory involvement must be carried out and appropriate supportive management and monitoring instituted, pending recovery. Potassium chloride may be administered orally or intravenously until weakness resolves. Mid-attack, TPP patients do not have a potassium deficit but rather an intracellular shift of their potassium. There is therefore a risk of rebound hyperkalemia on recovery as the potassium shift reverses. While patients recover twice as quickly with potassium treatment, up to 70 percent may experience rebound hyperkalemia. In practice this is rarely of clinical importance, but most authorities recommend giving lower doses of potassium (<50 mEq total). Potassium chloride does not always abort an attack of weakness in TPP. In cases of refractory weakness, propranolol administered intravenously or orally may be effective.

Patients should also be educated about TPP and its precipitants in order to prevent further attacks. They should avoid food and drink with high salt or carbohydrate content as well as alcohol. Formal exercise is best halted until the patient is euthyroid. Propranolol (40 mg daily) reduces the likelihood of further attacks until the euthyroid state is regained. Finally, definitive treatment of the hyperthyroidism and return of the patient to the euthyroid state stop further attacks of weakness altogether although, depending upon the underlying cause, it may take months for the euthyroid state to be achieved.

Myasthenia Gravis

A long-recognized association exists between thyroid disease and myasthenia gravis. There is no evidence that thyroid dysfunction causes myasthenia gravis, and the co-existence of the two conditions probably reflects an underlying predisposition to autoimmune disease.

A meta-analysis of nearly 25,000 patients with myasthenia gravis demonstrated that approximately 10 percent had thyroid autoantibodies, compared to 1 to 5 percent of the general population.[6]

Hyperthyroidism is diagnosed before or concurrent with the onset of myasthenia in roughly three-quarters of patients. In general, there are few unusual characteristics of either condition in terms of clinical features or management when the two occur in the same patient. The clinical expression may be mild, the likelihood of detectable acetylcholine receptor antibodies is reduced, and interestingly, patients who are hyperthyroid are more likely to have pure ocular myasthenia.

While control of the myasthenia may deteriorate with departure from the euthyroid state, treatment of the thyroid disorder does not have a predictable effect on the myasthenia. Dramatic increases in the severity of myasthenia have been reported following treatment of the thyroid disease, but this is uncommon. In some patients, an improvement in myasthenic weakness occurs after treatment of hyperthyroidism.

Peripheral Neuropathy

Peripheral neuropathy is rarely associated with hyperthyroidism, in contrast to its relatively common association with hypothyroidism. As a result, the pathophysiologic basis of any peripheral nerve dysfunction in hyperthyroidism is unclear, although a severe subacute motor axonal neuropathy induced by T3 hyperthyroidism and reversible on control of the hyperthyroid state has been described.

Mononeuropathies associated with hyperthyroidism are also relatively rare. Up to 5 percent of patients may have clinical and neurophysiologic features of carpal tunnel syndrome, the symptoms of which often resolve once control of the thyroid disease is achieved.

A rare acute thyrotoxic peripheral neuropathy resembling Guillain–Barré syndrome and causing paraplegia was first described by Charcot and termed Basedow paraplegia by Joffroy. The syndrome is acute in onset and presents as a flaccid, areflexic paraplegia with upper limbs much less affected than the lower limbs. There is sensory involvement in some cases and sphincter function is typically preserved. Electrophysiologic examination reveals a mixed sensorimotor peripheral neuropathy with demyelinating and axonal features; ultrastructural analysis in one case with sural nerve biopsy demonstrated axonal loss and myelin damage. Treatment usually results in a full recovery.

Corticospinal Tract Dysfunction

Signs of corticospinal tract dysfunction may be associated with thyrotoxicosis. Clinical features include spasticity and weakness, particularly affecting the lower limbs, as well as hyperreflexia, clonus at the ankles and knees, and extensor plantar responses. Occasionally, patients with upper motor neuron signs in the limbs also have had sensory abnormalities, including impaired vibration sensation and proprioception, upper motor neuron bladder disturbance, and urinary incontinence. A clinical picture similar to that of motor neuron disease has also been noted in patients with untreated hyperthyroidism. Treatment of the hyperthyroid state usually results in complete or near-complete recovery of the upper motor neuron signs.

A neurophysiologic correlate of these observations can be seen using transcranial magnetic stimulation of the motor cortex. Further histopathologic and neurochemical studies are required to define the pathophysiologic basis of corticospinal tract dysfunction in thyrotoxicosis.

Movement Disorders

CHOREA

Chorea is an unusual complication of hyperthyroidism and its association with the condition is not universally accepted. Some authors suggest that it is simply an exaggeration of the fidgetiness seen in thyrotoxicosis, whereas others believe that hyperthyroidism unmasks pre-existing and subclinical basal ganglia dysfunction. The problem appears to be more common in women, and the underlying cause of the hyperthyroidism is most commonly Graves disease. Choreiform movements typically involve the limbs, with the face, neck, or tongue affected in some cases. Less commonly, hemichorea and bilateral ballismus have been associated with thyrotoxicosis. The chorea usually resolves once hyperthyroidism has been controlled, but it can persist long after euthyroidism has been achieved.

The pathophysiologic basis of hyperthyroid chorea is unknown. Given that most cases occur in autoimmune hyperthyroidism, many have assumed that the associated chorea also has an autoimmune basis. It has been suggested that chorea may be mediated by the sympathetic nervous system because β-blockers may help to control symptoms. A disruption of striatal dopamine receptors may have some role and dopamine receptor antagonists, such as haloperidol, have been effective in the treatment of hyperthyroid chorea. Cases in which chorea develops when a patient is hyperthyroid, resolves on treatment, and then recurs when the patient once more becomes hyperthyroid due to, for instance, poor compliance, lend support to the idea that the chorea is a direct effect of high levels of thyroid hormone on the function of the basal ganglia.

TREMOR

Tremor is almost invariably seen in hyperthyroidism, so it is best considered a feature of the hyperthyroid state rather than a neurologic complication. The tremor seen in thyrotoxicosis can be considered an exaggerated physiologic tremor. It is postural, persists on movement (but is not present at rest), and has a frequency of 8 to 12 Hz. The tremor most commonly affects the outstretched hands and the tongue, but the lips and facial muscles may also be affected. Therapy with β-blockers provides relief, suggesting that increased β-adrenergic activity is likely to be responsible.

OTHER MOVEMENT DISORDERS

Other movement disorders that have been described in patients with hyperthyroidism include platysmal myoclonus and paroxysmal kinesogenic dyskinesia.

Thyroid-Associated Ophthalmopathy

Graves disease is an autoimmune condition in which antibodies to thyrotropin receptors are generated and bind to their antigen on follicular cells in the thyroid gland, inducing them to produce and release excess thyroid hormone, which causes hyperthyroidism. It is associated with two main extrathyroid complications: thyroid dermopathy (also known as pretibial myxedema) and thyroid-associated ophthalmopathy. Thyroid-associated ophthalmopathy, sometimes called Graves ophthalmopathy, is a potentially disfiguring and sight-threatening complication most commonly occurring in patients with hyperthyroidism due to Graves disease, or who have a past history of hyperthyroid Graves disease. While present in around 50 percent of patients, only 3 to 5 percent of those with Graves disease have severe, sight-threatening ophthalmopathy requiring aggressive therapeutic intervention. Graves ophthalmopathy is generally managed by ophthalmologists. Patients do, however, present to neurologists with complaints of visual loss or diplopia, and a summary focusing on these neurologic presentations and diagnosis therefore follows. More detailed descriptions can be found elsewhere.[10]

CLINICAL FEATURES

Symptoms and signs of Graves ophthalmopathy are usually bilateral and begin within 18 months of the onset of Graves hyperthyroidism. Ophthalmopathy in Graves disease may uncommonly appear to be unilateral (5 to 14%), although in these cases orbital imaging usually identifies subclinical involvement of the clinically unaffected eye. The onset of ophthalmopathy may precede the development of hyperthyroidism and may also develop some years after Graves disease has been diagnosed and treated. Whether Graves ophthalmopathy may be induced or existing eye disease worsened by radioiodine treatment for hyperthyroidism remains contentious. Smoking is clearly an independent and modifiable risk factor, and the more cigarettes smoked, the greater is the risk. The group at most risk appears to be patients treated with radioiodine who also smoke.

The majority of ocular symptoms and signs in Graves ophthalmopathy are the result of an increase in the amount of cushioning fat within the orbit and an enlargement of the extraocular muscles. Patients complain of a sensation of grittiness in the eyes, photophobia, and pressure or pain behind the eyes. The commonest features of Graves ophthalmopathy are periorbital and conjunctival edema and erythema (secondary to compression of orbital veins and resultant venous stasis), retraction of the upper eyelid (due to overactive sympathetic activity), and proptosis due to the increased volume of orbital contents (Fig. 18-1). If proptosis is severe, ptosis may occur. Proptosis is defined as measured exophthalmos greater than 2 mm above the upper normal limit. It is found in approximately 20 to 30 percent of patients with Graves disease. Proptosis serves to decompress the orbit—visual loss due to compressive optic neuropathy occurs more often in those with little or no compensatory proptosis. Apart from any cosmetic problems associated with proptosis, failure of the eyelids to close completely may result in sight-threatening exposure keratopathy.

Extraocular muscle involvement leading to ophthalmoparesis is clinically apparent in 10 to 15 percent of patients with Graves hyperthyroidism. Orbital imaging demonstrates enlargement of the extraocular muscles in 60 to 98 percent of these patients (Fig. 18-2). Patients may complain of blurred vision with binocular gaze, diplopia that may be continuous or intermittent, or a pulling sensation on attempted upgaze. For reasons that are not understood, there is preferential involvement of the inferior and medial rectus muscles.

Optic nerve compression occurs in fewer than 5 percent of patients with Graves disease. It results from apical crowding of the orbit due to enlargement of the extraocular muscles and excess orbital connective tissue. Early recognition is important to prevent loss of vision, and since there may not always be accompanying proptosis and orbital inflammation, careful examination for optic disc swelling and impaired color vision is paramount, together with radiologic assessment for optic nerve compression.

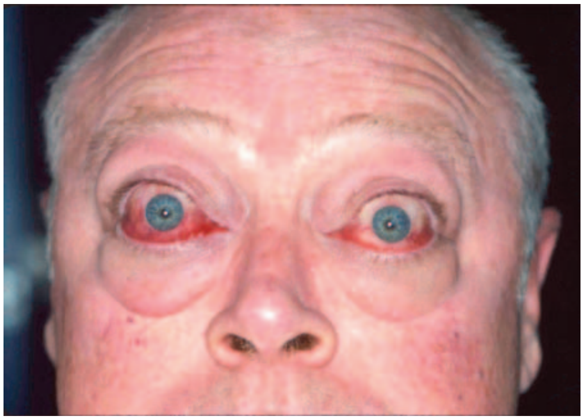

FIGURE 18-1 ■ Fifty-year-old man with thyroid eye disease, showing periorbital edema, conjunctival injection, proptosis, and eyelid retraction. (Courtesy of Jonathan Horton, MD, PhD.)

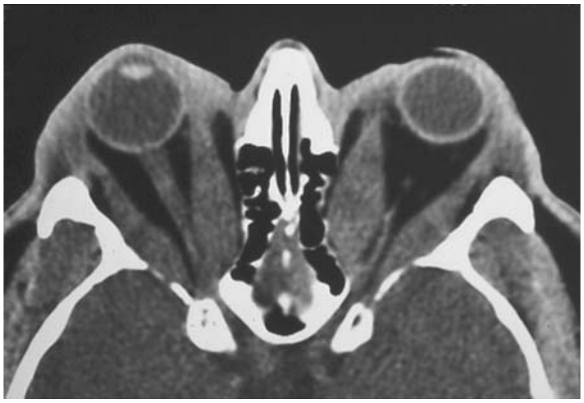

FIGURE 18-2 ■ Axial computed tomographic scan of the patient in Fig. 18-1, showing massive enlargement of the horizontal rectus muscles and soft-tissue edema in each orbit, causing compression of the optic nerves. (Courtesy of Jonathan Horton, MD, PhD.)

DIAGNOSTIC TOOLS

Diagnosis is largely based on clinical features, with orbital imaging used to confirm the diagnosis and exclude other entities, especially in apparently unilateral cases. As levels of antithyrotropin antibody correlate with disease severity, these should be measured and thyroid function tests performed. In patients with Graves orbitopathy, MRI is the imaging modality of choice and can reveal disease activity with interstitial edema within the extraocular muscles. The presence of such observations, rather than the fibrotic changes associated with end-stage disease, may direct treatments toward immunomodulatory therapies. MRI may also be used to assess response to such interventions. By contrast, CT is suited to the assessment of bony periorbital structures and is thus the technique of choice for planning of CT-guided orbital decompression surgery. Amplitude reduction on pattern electroretinogram may be a sensitive measure for demonstrating early impairment of optic nerve function, as may measurements of visual evoked potentials.

PATHOGENESIS

Although significant progress has been made in understanding the pathogenesis of Graves ophthalmopathy, there remain a number of contentious issues and unanswered questions.[10] Environmental, immune, and genetic factors are all likely to play a role. It is widely accepted that antithyrotropin antibodies are pathogenic in Graves ophthalmopathy and that their target within the eye is orbital fibroblasts, which express the thyrotropin receptor to a greater extent than do orbital fibroblasts in unaffected subjects. Interaction of these pathogenic antibodies with thyrotropin receptors triggers an inflammatory cascade within the orbit, resulting in the expansion of orbital adipose tissue. Antithyrotropin antibodies are not the only pathogenic antibodies in Graves ophthalmopathy. The best supported of several additional candidates are antibodies to insulin-like growth factor-1. It seems likely that many of the other antibodies detected in Graves ophthalmopathy will turn out to be secondary markers of the orbital immune-mediated reaction rather than pathogenic effectors.

TREATMENT

A consensus statement on the management of thyroid-associated ophthalmopathy was released in 2008 and has been addressed in review articles.[10] In summary, there is currently no recommended preventive therapy and the condition is usually only treated when symptoms are severe or vision is threatened. In ophthalmopathy where there is evidence of active inflammation, corticosteroids and orbital radiotherapy may be used. Sight-threatening keratopathy due to proptosis and optic neuropathy due to apical crowding are treated surgically with orbital decompression. Some authorities use a 3-month course of corticosteroids starting immediately after radioiodine treatment in order to prevent development or exacerbation of Graves ophthalmopathy. Treatment of dysthyroid strabismus is surgical once Graves disease has burnt out and the ophthalmoparesis is stable. Prism glasses are an alternative in those preferring not to undergo surgery. During the active phase of the disease, botulinum toxin may also be used to improve strabismus. A number of immunomodulatory therapies have been suggested for use in Graves ophthalmopathy.[10]

Encephalopathy

Florid thyrotoxic encephalopathy, sometimes referred to as "thyroid storm," is seen less often now that active monitoring and treatment of hyperthyroidism is undertaken. Its clinical features and treatment are well described.[11] Thyroid storm is thought to make up 1 to 2 percent of thyroid-related admissions to hospital. Precipitating factors include radioactive iodine therapy, surgery (either thyroid or nonthyroid), trauma, pregnancy, and intercurrent illness. While there is no consensus definition of what constitutes thyroid storm, four groups of symptoms dominate the clinical picture—fever, tachycardia, CNS dysfunction, and gastrointestinal symptoms. Fever is high and associated with profound sweating. Patients may develop supraventricular tachyarrythmias including atrial fibrillation with consequent cardiac failure or embolic stroke. Diarrhea and vomiting are common, and patients may have jaundice. Biochemically, thyroid storm may be indistinguishable from uncomplicated thyrotoxicosis, making its diagnosis a clinical one. CNS symptoms may be prominent. Affected individuals are commonly confused or agitated and may present with frank psychosis. The patient's level of consciousness may deteriorate, with the development of coma sometimes associated with seizures and status epilepticus, bulbar weakness, and corticospinal tract signs.

The mortality of thyroid storm remains over 10 percent, so patients should be managed in an ICU.[11] Successful treatment depends on early recognition and aggressive intervention. Treatment is aimed at: (1) reducing production and secretion of thyroid hormones by the thyroid gland, for which antithyroid medication and sometimes iodine are used; (2) reducing the effects of the excess thyroid hormone on target organs in the periphery using β-blockade; (3) reversing systemic problems such as fever and cardiovascular compromise; and (4) treating any precipitating factor such as systemic infection. Administration of corticosteroids is suggested in recognition of adrenal axis dysfunction. Plasmapheresis has been employed occasionally to reduce levels of thyroid hormone.

Seizures

Seizures are a relatively frequent complication of metabolic encephalopathy in general, but are not commonly seen as a complication of thyrotoxicosis. A retrospective analysis of over 3,000 patients diagnosed with hyperthyroidism revealed that only 0.2 percent experienced seizures not attributable to other causes.[12] In these instances, generalized tonic-clonic events were most common. The cause of the hyperthyroidism appears not to be important, with seizures happening even in the context of hypothyroidism overtreated with thyroxine. The etiology of thyrotoxic seizures is unknown.

A range of nonspecific EEG abnormalities may be seen in patients with hyperthyroidism, including generalized slow activity and an excess of fast activity.[12] EEG changes usually improve when the thyrotoxic state is controlled.

Mental and Psychiatric Disorders

Minor mental disturbances are almost uniformly found in patients presenting with untreated hyperthyroidism. Complaints of insomnia and impairment of concentration and attention are common. Patients' acquaintances frequently describe irritability, emotional lability, and capricious behavior. Agitated delirium, presenting with confusion, restlessness, hyperkinesia, and an apathetic state with lethargy and depression may occur in thyrotoxic patients; this often resolves with successful treatment of the hyperthyroidism. Both psychosis and affective disorders have been described, and there is a significant overlap between symptoms of hyperthyroidism and that of depression-anxiety. It is important to be alert to the possible psychiatric manifestations of thyroid dysfunction and to reassess patients once they become euthyroid.

Stroke

The association between thyroid disease and stroke has been thoroughly reviewed elsewhere.[13] Atrial fibrillation may develop in 10 to 15 percent of patients with hyperthyroidism and it has been suggested that 10 to 40 percent of patients with thyrotoxic atrial fibrillation have embolic events, the majority of which are cerebral. Whether thyrotoxic patients in atrial fibrillation have a higher embolic risk than euthyroid patients with chronic atrial fibrillation is uncertain. Prognostically, a meta-analysis of observational studies concluded that following an ischemic stroke subclinical hypothyroidism was associated with a better outcome, and low T3 and free T3 (fT3) levels were correlated with a worse outcome. Conversely, elevated T3 and fT3 values were associated with a better outcome, while elevated T4 was associated with a poor prognosis. Thyroid hormone is thought to have both a neurotoxic and neuroprotective effect which may explain the complex relationship described.[13]

Evidence for associations between hyperthyroidism and rarer causes of stroke is sparse. There is a possible link between moyamoya syndrome and hyperthyroidism, secondary to an increased level of thyroid antibodies.

Hashimoto Encephalopathy

Hashimoto encephalopathy (HE) is a relatively rare condition arising as a complication of Hashimoto thyroiditis. In Hashimoto thyroiditis, an antibody-mediated attack on the thyroid gland eventually brings about hypothyroidism although there may be an initial, transient hyperthyroidism and a period of intervening euthyroidism. HE typically occurs in patients with Hashimoto thyroiditis who are hypothyroid or euthyroid but it can, less often, occur in hyperthyroid patients. For this reason, HE is not believed to be a consequence of the patient's thyroid status. Numerous case studies of HE exist, as well as a few small case series.[14] The rarity of the disorder and the absence of consensus diagnostic criteria mean that qualifying clinical features and even the existence of HE as an entity are ongoing subjects of debate.

CLINICAL FEATURES

Clinical features of HE include relapsing episodes of encephalopathy, seizures, and sometimes superimposed stroke-like neurologic deficits. The encephalopathy ranges from confusion to coma with an acute or subacute onset, but it may also present insidiously as gradual cognitive decline. In adults it may be confused with dementia, and in children it can manifest as a falling-off of school performance. Seizures in HE may be focal or generalized, and status epilepticus can occur. Patients have high levels of antithyroid antibodies and the episodes are responsive to treatment with corticosteroids.

Patients with HE are usually euthyroid but may be hypothyroid. Patients may have encephalopathy with antithyroid antibodies, an abnormal EEG, and hyperthyroidism and, if so, are termed thyrotoxic Hashimoto thyroiditis. Women are affected by HE more than men, and while the typical age of onset is around 40 years, it can occur in children. The encephalopathy is generally accepted as essential for a diagnosis of HE to be contemplated but there is less agreement about associated features. Cases of HE featuring aphasia, ataxia, myoclonus, tremor, headache, psychosis, and visual hallucinations have all been reported.

PATHOPHYSIOLOGY

The presence of antithyroid antibodies is a prerequisite for the diagnosis of HE, but it remains unclear whether these antibodies are pathogenic effectors or simply proxy markers of the disease. The fact that antithyroid antibodies are associated with diverse and unrelated conditions and are found in a proportion of the healthy population argues against a direct role. Few reports have found HE-specific CNS epitopes to which antithyroid antibodies bind. Antithyroid peroxidase antibodies have been found to bind to cerebellar astrocytes in HE but not Hashimoto thyroiditis, although the significance of this finding is unclear. The presence of lymphocytic infiltration of CNS vessels implies that the disorder invokes a vasculitic process, but the largely favorable outcome of this rare condition means that few cases come to autopsy when the condition is active.

DIAGNOSIS

Differential Diagnosis

The lack of clear diagnostic criteria and the variety of neurologic symptoms and signs reported in addition to encephalopathy mean that HE should be considered in the differential diagnosis of all cases of encephalopathy in which an alternative explanation is not quickly evident. Although HE is rare, it is treatable. Thyroid antibodies therefore should be checked as part of the standard laboratory evaluation of encephalopathy. In a series of 20 patients with a final diagnosis of HE, all were initially given another diagnosis including dementia, encephalitis, stroke, Creutzfeldt–Jakob disease, and migraine.[14]

Antithyroid Antibodies

Antibodies directed against thyroid antigens are a defining feature of HE. Despite this, there is little consensus about which antithyroid antibodies are associated with HE and whether they have a role in pathogenesis. Antithyroid peroxidase (anti-TPO) antibodies are elevated in almost all cases of HE. They are also raised in other nonthyroid autoimmune disorders and in some healthy controls. Antibodies against thyroglobulin (anti-TG) are often found in cases of HE but less commonly than are anti-TPO antibodies. Anti-TG antibodies are also found in a proportion of healthy subjects without thyroid disease. Anti-α-enolase antibodies have also been found in the serum of some patients with HE.

Cerebrospinal Fluid

The most common finding in HE is a raised protein concentration, although a mild pleocytosis and oligoclonal bands (not present in serum) or an elevated IgG index are also common.

Imaging

Although CT of the brain is typically normal, MRI in HE has shown diffuse white matter abnormalities in up to half of patients, and these may resolve with treatment. A variety of other abnormalities have been reported in individual cases, but no HE-defining abnormality has been identified and some patients may have normal imaging.[14] The few reports of single photon emission CT in HE document focal hypoperfusion, generalized hypoperfusion, or no abnormalities at all. Cerebral angiography is generally normal, showing no evidence of large-vessel vasculopathy.

Electroencephalography

Most patients have an abnormal EEG. Generalized slowing is the commonest abnormality, but triphasic waves and periodic complexes have also been reported. No HE-specific EEG features have been identified.

TREATMENT

There is reasonable evidence that the vast majority of episodes of HE respond to treatment with corticosteroids, while only two-thirds of patients respond if treated solely with levothyroxine. Plasmapheresis can also be effective, including in cases resistant to corticosteroids. Treated, the prognosis of HE is generally good. It is therefore sensible to consider a trial of corticosteroids in an encephalopathic patient with antithyroid antibodies and no other obvious underlying cause, once CNS infection has been excluded.

MISCELLANEOUS ASSOCIATIONS BETWEEN NEUROLOGIC DISORDERS AND THYROID DYSFUNCTION

Endocrine Dysfunction in Long-Term Survivors of Primary Brain Tumors

Endocrine dysfunction, including hypothyroidism, is a frequent and often overlooked long-term complication of radiotherapy for primary brain tumors, with a significant impact on the well-being of patients. One-quarter of patients may develop hypothalamic hypothyroidism. Hypothalamic hypogonadism in males and hyperprolactinemia and oligomenorrhea in female patients are also recognized. Endocrine function should therefore be evaluated periodically in long-term survivors of primary brain tumors treated with radiotherapy.

Multiple Sclerosis and Thyroid Disease

Thyroid disease has been found to be at least three times more common in women with multiple sclerosis, and this is largely a hypothyroid burden. Recent reports have also documented thyroid-related complications in patients treated with alemtuzumab, which alters the immune response from the Th1 phenotype, suppressing disease activity in multiple sclerosis but permitting the generation of antibody-mediated thyroid disease.[15]

Recurrent Laryngeal Nerve Palsy

Both malignant disease of the thyroid gland and thyroidectomy may be associated with hoarseness and other bulbar symptoms due to damage to the recurrent laryngeal nerve. Invasion of the recurrent laryngeal nerve by thyroid carcinoma can be accurately predicted by the finding of effaced fatty tissue on MR imaging.

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CHAPTER

19

Diabetes and the Nervous System

KAYLYNN PURDY ■ DOUGLAS W. ZOCHODNE

NEUROLOGIC FEATURES OF HYPERGLYCEMIA AND HYPOGLYCEMIA
  Diabetic Ketoacidosis
  Nonketotic Hyperosmolar Syndrome
  Hypoglycemia
PERIPHERAL NEUROPATHIES
  Diabetic Polyneuropathy
    Testing
    Differential Diagnosis
    Pathogenesis
    Treatment
  Focal Mononeuropathies
    Carpal Tunnel Syndrome
    Ulnar Neuropathy at the Elbow
    Meralgia Paresthetica
    Intercostal or Truncal Radicular Neuropathies
    Oculomotor Neuropathy
    Diabetic Lumbosacral Plexopathy
    Other Focal Neuropathies
  Autonomic Neuropathy
CENTRAL NERVOUS SYSTEM COMPLICATIONS
  Cognitive Dysfunction
  Cerebral Infarction and Vascular Dementia
  Alzheimer Disease
NEUROPATHIC PAIN
  Pathophysiology
  Treatment
    Specific Therapeutic Agents

Both type 1 and type 2 diabetes mellitus commonly target the nervous system. In the peripheral nervous system, complications include polyneuropathies and focal neuropathies. In the central nervous system (CNS), diabetes may be associated with cognitive decline, leukoencephalopathy, and heightened risk of both stroke and dementia. Acute changes in blood glucose levels are also associated with neurologic signs and symptoms. This chapter summarizes the acute and chronic neurologic complications of diabetes mellitus. For a detailed discussion of diabetes and the nervous system, with relevant reference citations, readers are also referred to a recent monograph on the topic.[1]

NEUROLOGIC FEATURES OF HYPERGLYCEMIA AND HYPOGLYCEMIA

Diabetic Ketoacidosis

Diabetic ketoacidosis in patients with type 1 diabetes is a medical emergency that may present with neurologic signs and symptoms.[2] Anorexia, lethargy, thirst, polyuria, vague abdominal pain, and Kussmaul respiration are followed by confusion and a decreased level of consciousness. Rarely, diabetic ketoacidosis accompanies a primary CNS infection, such as bacterial meningitis. Cerebral edema complicates diabetic ketoacidosis and may present with headache, papilledema, and bilateral abducens neuropathies. It may develop on presentation or during correction of the metabolic disorder. Secondary complications include cerebral infarction, cerebral venous sinus thrombosis, and compression neuropathies.

Nonketotic Hyperosmolar Syndrome

Neurologic symptoms and signs may also reflect a nonketotic hyperosmolar syndrome, defined as a blood glucose level exceeding 33 mmol/L (600 mg/dL) and a plasma osmolarity greater than 320 mOsm/L, without accompanying acidosis or ketonemia. Polyuria, polydipsia, thirst, fatigue, and overall weakness are

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general symptoms; neurologic signs include decreased level of consciousness, hemiplegia, aphasia, brainstem abnormalities, dystonia, chorea, and seizures. The seizures are often focal and can include tonic, movement-induced, or continuous forms (e.g., epilepsia partialis continua). Unusual neurologic features are visual symptoms, hallucinations, hemichorea, tonic eye deviation, nystagmus, abnormal pupils, and meningeal signs. The correction of hyperglycemia may be more effective than using antiepileptic agents to treat the seizures.

Hypoglycemia

Hypoglycemia most often presents with altered neurologic function.[2] In diabetic subjects, hypoglycemia is common in the setting of insulin use. A high index of suspicion is required as patients may present with focal neurologic signs or seizures. Hypoglycemia is defined as a plasma glucose concentration less than 2.7 mmol/L (50 mg/dL), a level associated with a decline in cognitive function. Premoni-tory systemic symptoms include anxiety, tachycardia, perspiration, nausea, and tremor, but these signs may be absent in patients taking β-adrenergic-blocking medications or in patients with autonomic neuropathy. Early neurologic symptoms are decreased attention and concentration, drowsiness, poor memory, disorientation, behavioral changes, clumsiness, and tremor. Patients may progress to experience seizures and loss of consciousness. Seizures may be focal or generalized and may lead to status epilepticus. Rapid detection through expectant testing and early treatment are essential. Severe untreated hypoglycemia is associated with diffuse cortical, basal ganglia and dentate gyrus damage, leading to permanent disability.

PERIPHERAL NEUROPATHIES

Diabetes mellitus targets the peripheral nervous system in several ways. Polyneuropathy is a chronic, symmetric disorder that targets the distal terminals of axons first. Focal or localized neuropathies of a single plexus or nerve, also known as mononeuropathies, are also common and develop from mechanical compression, ischemia, or other, less well-defined causes. Autonomic neuropathy is the other major category of peripheral nervous system dysfunction in these patients.

Diabetic Polyneuropathy

Diabetic polyneuropathy is the most common form of peripheral neuropathy.[3,4] With detailed evaluation, approximately 50 percent of both type 1 and type 2 diabetic subjects have evidence of polyneuropathy. Symptomatic polyneuropathy may occur in a smaller proportion, estimated as approximately 15 percent of these patients.[5] Lower prevalence numbers have been derived from studies of hospitalized patients or utilizing exclusively clinical signs of polyneuropathy. Polyneuropathy is most often sensory, or sensorimotor but with lesser motor involvement. Positive sensory symptoms are common and include prickling, tingling, "pins and needles," burning, crawling, itching, electric, sharp, jabbing, and tight sensations in the legs, feet, hands, and fingers. Warm stimuli may be inappropriately perceived as cold, and cold stimuli as warm or hot. Nocturnal burning of the feet accompanies allodynia (the generation of pain or discomfort from normally innocuous stimuli). Many of these symptoms are associated with pain, sometimes severe or intractable, as discussed later.

Symptoms are generally symmetric and initially confined to the toes, with later spread to more proximal parts of the feet and legs and to the fingers (Fig. 19-1). Negative symptoms include loss of sensation to light touch, pinprick, and hot and cold. In more severe diabetic polyneuropathy, loss of protective sensation predisposes patients to the development of foot ulcers. Additional factors that promote foot ulceration include loss of sweating, abnormal foot architecture from muscle wasting, delayed healing, and both macrovascular (atherosclerosis) and microvascular disease.

There is a stocking-and-glove pattern of sensory symptoms and loss. Motor involvement is less common in early diabetic polyneuropathy but may eventually lead to distal weakness of foot and toe dorsiflexion, predisposing patients to falls. Weakness accompanies wasting of intrinsic foot muscles. Symptoms from concurrent abnormalities of the autonomic nervous system are common. They include erectile dysfunction (ED) in men, distal loss of sweating, orthostatic dizziness, and bowel and bladder dysfunction.

A detailed neurologic examination provides a low-cost, patient-interactive means of direct evaluation. While some variation in findings, especially in patients with early disease, is expected, the examination remains the gold standard for

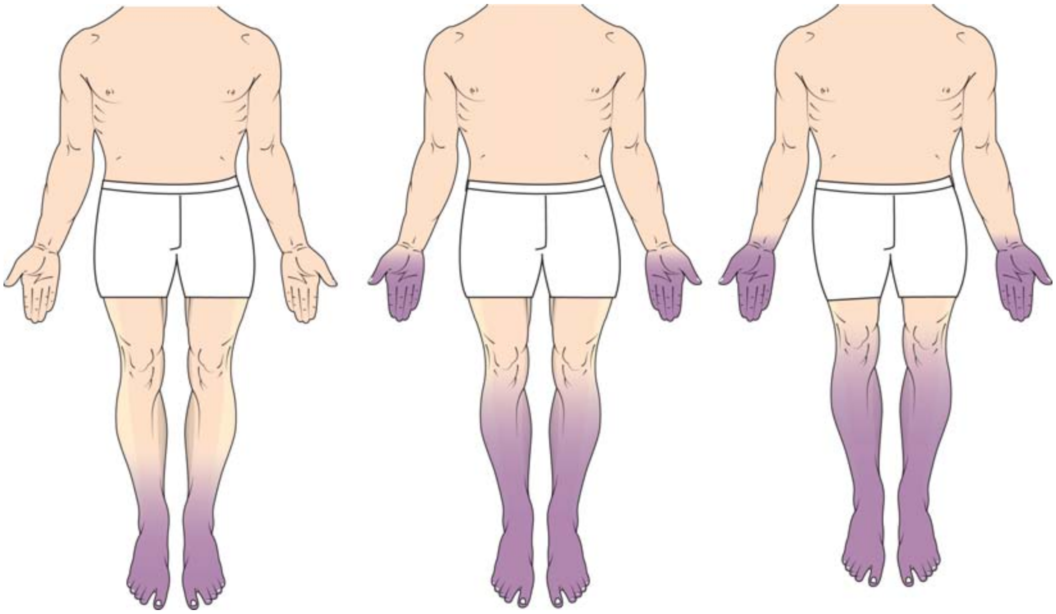

FIGURE 19-1 ■ Illustration of progressive stocking-and-glove sensory changes in a patient with progressive diabetic polyneuropathy. Sensory symptoms and signs begin in the distal territories of sensory nerves in the toes and fingers, with a gradual spread proximally. (From Zochodne DW, Kline G, Smith EE, et al: Diabetic Neurology. Informa Healthcare, New York, 2010, with permission.)

diagnosis and is not replaced by quantitative methods or electrophysiologic evaluation, which are considered ancillary tests.

On sensory examination, there is distal loss of sensation to light touch, pinprick, cold, and vibration with a 128-Hz tuning fork. Some patients with more dense sensory loss are unable to distinguish sharp (pinprick) from dull (analgesia) or to feel light touch at all (anesthesia). The Semmes–Weinstein (10 g) monofilament test is a useful adjunct to the neurologic examination. The filament is pressed against the skin over the dorsum of the great toe or other selected areas of the foot until it bows into a C shape for 1 second, and the patient is asked whether the stimulus is felt. The Rydel–Seiffer tuning fork provides semiquantitative information about vibratory sensory perception and can contribute to grading the severity of the polyneuropathy. Vibratory loss may involve the distal toes, the foot below the ankle, or more extensive territories, depending on its severity. Testing for proprioceptive abnormalities in the toes is often normal except when the polyneuropathy is severe.

Distal motor wasting, such as in the extensor digitorum brevis muscle, and associated weakness especially involving foot and toe dorsiflexion, usually accompany more severe sensory loss. Patients may have foot ulcers or, less commonly, a destructive arthropathy from repetitive injury, known as a Charcot joint. Loss of the muscle stretch reflex at the ankle is common in early diabetic polyneuropathy; all the muscle stretch reflexes may be lost with more severe neuropathies. The feet may be dry from loss of sweating. Patients with concurrent atherosclerosis have loss of distal pulses and sometimes femoral bruits. Orthostatic vital signs should be assessed; in patients with involvement of the autonomic nervous system, a decline of 20 mmHg or more in the systolic blood pressure or 10 mmHg in diastolic pressure indicates postural hypotension.[3]

Diabetic polyneuropathy has been divided into subcategories depending on whether large- or small-fiber involvement occurs. In large-fiber polyneuropathy, there is more prominent loss of sensation to light touch, vibration, and proprioception. Patients may have accompanying ataxia of gait. In small-fiber polyneuropathy, pinprick and thermal appreciation are impaired and autonomic dysfunction is common, as is neuropathic pain, especially at night. Neuropathic pain can accompany other forms of diabetic polyneuropathy as well.

Several scales have been developed to grade the severity of diabetic polyneuropathy for clinical trials, including the Modified Toronto Neuropathy Scale, the Utah Neuropathy Scale, the Michigan Neuropathy Scale, and the Mayo Clinic diabetic polyneuropathy classification.

TABLE 19-1 ■ Differential Diagnosis of Diabetic Polyneuropathy

Vitamin Deficiency

B vitamin deficiency (e.g., vitamin B_1 or B_{12})
Vitamin E deficiency

Infectious and Inflammatory

Human immunodeficiency virus (HIV) infection
Leprosy
Lyme disease
Hepatitis C infection
Guillain—Barré syndrome
Chronic inflammatory demyelinating polyneuropathy
Anti-MAG neuropathy
Lewis—Sumner syndrome
Distal demyelinating sensory neuropathy
Neuropathies associated with monoclonal gammopathies
Primary biliary cirrhosis
Sarcoidosis

Endocrine

Hypothyroidism
Acromegaly (with diabetes)

Drugs and Toxins

Antibiotics (e.g., metronidazole, isoniazid, nitrofurantoin)
Antineoplastic agents (e.g., vincristine, vinblastine, cisplatinum)
Ethanol (often in association with thiamine deficiency)
Organophosphate poisoning
Pyridoxine
Antiretroviral therapies
Interferon-α
Anti-TNF-α treatment for inflammatory disorders
Sinemet (via vitamin B_{12} deficiency)
Metformin (via vitamin B_{12} deficiency)
Others

Metabolic

Hepatic cirrhosis
Renal failure
Critical illness (sepsis and multiorgan failure)
Acquired amyloidosis
Bariatric surgery

Congenital/Inherited

Charcot—Marie—Tooth disease (multiple subtypes)
Hereditary susceptibility to pressure palsies
Hereditary amyloidosis
Hereditary sensory and autonomic neuropathies

Vascular

Necrotizing vasculitis (confined to peripheral nerves or in association with systemic vasculitis)
Severe peripheral vascular disease
Cryoglobulinemia (with or without hepatitis C infection)

Neoplastic

Paraneoplastic neuropathies (anti-Hu, anti-Ma, others)
Leptomeningeal carcinomatosis, lymphomatosis, gliomatosis
Angioendotheliosis
Primary intraneural lymphoma

TESTING

In patients with established diabetes mellitus and typical symptoms of polyneuropathy, extensive additional testing may not be required. Exclusion of other causes of sensory polyneuropathy can be accomplished through judicious screening for hypothyroidism, vitamin B_{12} deficiency, monoclonal gammopathy, and ethanol abuse. Table 19-1 is an extensive list of alternative diagnoses that may resemble diabetic polyneuropathy.

Electrophysiologic testing is recommended for patients with unexpectedly severe or atypical forms of polyneuropathy including motor-predominant disease, rapidly progressive symptoms, asymmetric signs, or when another neuromuscular condition is suspected. It is important to choose a laboratory with appropriate certification, training, and experience in performing these techniques. Two major components are usually performed: nerve conduction studies and needle electromyography (EMG). In patients with only sensory symptoms and findings, nerve conduction studies alone may be sufficient. Initial changes in patients with diabetic polyneuropathy include reductions in the amplitude and conduction velocity of the sural sensory nerve action potential (SNAP) recorded from behind the ankle. Slowing of conduction velocity in fibular (peroneal) motor axons detected by recording over the extensor digitorum brevis muscle of the foot is an additional early abnormality. In severe neuropathy, there may be widespread loss of SNAPs and diffuse mild-to-moderate conduction velocity slowing in a number of motor and sensory nerve territories (Fig. 19-2). In some patients with severe involvement, these findings may resemble the changes expected in a demyelinating polyneuropathy such as chronic inflammatory demyelinating polyneuropathy (CIDP), but it is usually possible to distinguish this condition. In CIDP, there are many more striking electrophysiologic features of primary demyelination such as motor conduction block or dispersion of compound muscle action potentials (CMAPs).

Loss of motor axons in more advanced diabetic polyneuropathy is detected by a decline or loss of

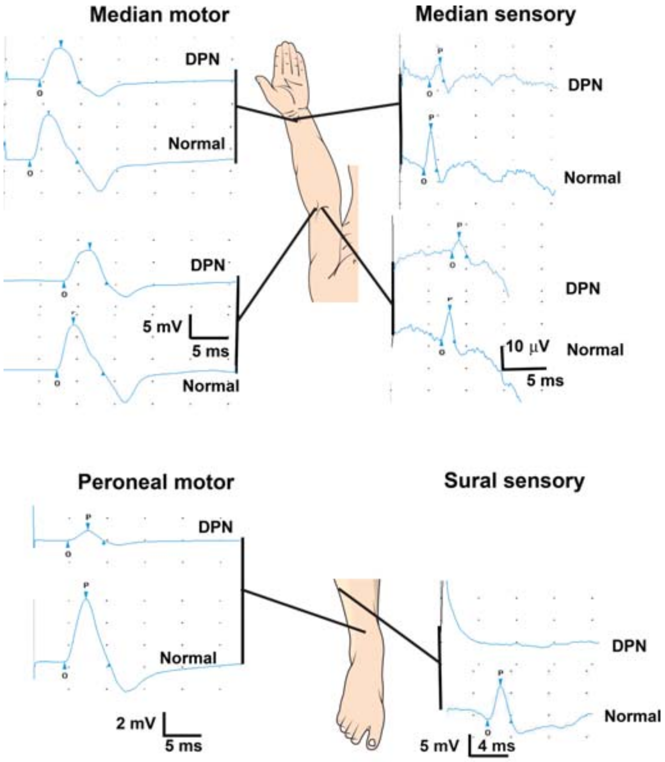

FIGURE 19-2 ■ Examples of nerve conduction abnormalities in a patient with moderately severe diabetic polyneuropathy (DPN) compared with waveforms in a normal subject. Note the decreased amplitude and prolonged latency of compound muscle action potentials and sensory nerve action potentials. The sural sensory nerve action potential is absent. Lines indicate nerve stimulation sites (recording site for the median motor nerve is the abductor pollicis brevis; for the median sensory nerve, the index finger; for the fibular [peroneal] motor nerve, the extensor digitorum brevis; and for the sural nerve, behind the lateral ankle). (From Zochodne DW, Kline G, Smith EE, et al: Diabetic Neurology. Informa Healthcare, New York, 2010, with permission.)

CMAPs, initially in the lower and then the upper limbs. In these patients, needle EMG may detect abnormal spontaneous activity, including fibrillation potentials and positive sharp waves, in muscles that have undergone denervation. In the setting of partial loss of motor axons, remaining fibers sprout and innervate adjacent denervated muscle fibers. When activated, the motor unit action potentials recorded from these partially denervated muscles are enlarged but reduced in number, indicative of chronic denervation and reinnervation. Electrophysiologic testing is also valuable in identifying superimposed entrapment or compression neuropathies, which are discussed later.

To reproducibly detect or track sensory changes, quantitative sensory testing (QST) using a computer interface may be used. While its chief utility is currently for clinical trials, it may offer early detection should better therapy for diabetic polyneuropathy emerge. QST equipment is available from several manufacturers and most use calibrated electronic interfaces to measure thermal thresholds (warm, cold), pain, touch-pressure, and vibration. As expected, these thresholds in the feet are raised in diabetic polyneuropathy.

Specific testing of the autonomic nervous system is available for evaluating co-existing autonomic involvement (see Chapter 8). In some patients with diabetes mellitus, however, prominent and apparently selective autonomic damage occurs without polyneuropathy, as discussed later. Since postganglionic autonomic axons are unmyelinated, autonomic function testing may detect small-fiber forms of diabetic polyneuropathy.

Two additional forms of testing, not in routine clinical use for diabetic polyneuropathy, also evaluate small-fiber involvement. These include skin biopsy, using a 3-mm punch to count the number of epidermal axons, and corneal confocal microscopy, which provides a noninvasive measure of unmyelinated axons in the cornea and complements skin biopsy.[6]

Biopsy of the sural nerve is not indicated for the routine evaluation of diabetic polyneuropathy and should be reserved for the diagnosis of unusual or progressive neuropathies that are atypical and suspected to be from another cause. In diabetes, sural nerve biopsies show loss of myelinated and unmyelinated axons that can accompany microvascular basement membrane thickening, endothelial cell reduplication, or vessel occlusion. Sural nerve biopsies leave the patient with a sensory deficit and therefore should be performed judiciously.

Cerebrospinal fluid (CSF) examination is not indicated routinely for typical diabetic polyneuropathy, although when performed it may show an elevated CSF protein concentration without pleocytosis.

Imaging studies are used to exclude spinal cord disease, spinal stenosis, or other central disorders with symptoms that may resemble diabetic polyneuropathy. There are no specific imaging characteristics of diabetic polyneuropathy although newer approaches—including ultrasound—are under evaluation.

Differential Diagnosis

A number of neurologic disorders may resemble diabetic polyneuropathy. Other polyneuropathies with prominent sensory involvement are listed in Table 19-1. A detailed neurologic examination is essential to exclude other syndromes in diabetic patients; for example, spinal cord disease may present with limb tingling and numbness, but other signs of upper motor neuron dysfunction are usually present on examination. Lesions at the cervicomedullary junction may cause sensory symptoms that begin in one limb and then progressively involve all four limbs. "Pseudoneuropathy" is a term used to describe the combination of lower limb sensory symptoms from spinal stenosis with upper limb tingling caused by carpal tunnel syndrome. It is important to identify patients with CIDP because they may respond to immunomodulatory therapies.

Pathogenesis

A number of mechanisms have been considered in the pathogenesis of diabetic peripheral neuropathy, all with limited definitive evidence, and they are discussed elsewhere in recent reviews.[7,8] Most have been evaluated in rat and mouse models of diabetes. Excessive flux of polyols (sugar alcohols), especially sorbitol, through the aldose reductase pathway is one such proposed mechanism. Aldose reductase inhibitors or protein kinase C inhibitors that interrupt this pathway have had limited clinical benefits, problematic side effects, or lack of penetration into the peripheral nervous system. Free radical oxidative/nitrergic stress and mitochondrial dysfunction along with impaired antioxidant defenses likely contribute to neuronal damage. Diabetic microangiopathy may lead to ischemic damage of neurons and axons. We have suggested that microangiopathy contributes to diabetic polyneuropathy later in the illness rather than serving as a primary trigger.

Trophic mechanisms that support neurons are impaired in diabetes. To date, separate clinical trials with nerve growth factor, neurotrophin-3, and brain-derived neurotrophic factor have been disappointing. In each case, the ability to protect all types of peripheral neurons targeted by diabetes has been limited. An intriguing alternative is insulin itself, an important growth factor which is neurotrophic; its receptors are widely expressed on most neurons of the peripheral nervous system. Novel forms of near-nerve or intranasal insulin have improved experimental diabetic neuropathy.

Treatment

Despite extensive experimental work, no therapy is available to arrest or reverse diabetic polyneuropathy. Tight control of hyperglycemia reduces the incidence of polyneuropathy and its progression. Daily foot inspection for injuries and early ulceration is recommended. There is no role for multiple nerve decompressive procedures to treat diffuse diabetic polyneuropathy. Treatment for neuropathic pain is discussed later.

Focal Mononeuropathies

Focal neuropathies involving single peripheral nerves are common in diabetes. Many of these mononeuropathies develop at sites of entrapment or compression. Others are of uncertain origin or may develop from nerve trunk ischemia.

Carpal Tunnel Syndrome

Carpal tunnel syndrome arises from compression of the median nerve at the wrist beneath the transverse carpal ligament, often following repetitive use of the wrist. It is characterized by tingling, pain, and numbness in the thumb, index, and middle fingers, especially at night or on awakening. Asymptomatic carpal tunnel syndrome (electrophysiologic diagnosis) can be detected in 20 to 30 percent of diabetics but symptoms are present only in approximately 6 percent.[5] It is the most common entrapment neuropathy overall and the most common type in diabetic subjects. Women are affected more often than men and the dominant hand is involved more often than the nondominant hand.

Tinel sign (tapping over the median nerve at the wrist evokes positive sensory symptoms that resemble the patient's symptoms distal to the wrist) and Phalen sign (reproduction of tingling by having both wrists flexed and held against each other for 1 minute) may be present, but are nonspecific and insensitive. In mild carpal tunnel syndrome, clinical signs may be absent. Later, sensory loss may occur in the median nerve territory. In more severe carpal tunnel syndrome, weakness and wasting of the abductor pollicis brevis develops. Electrophysiologic testing helps to distinguish the disorder from radiculopathy or other upper limb neuropathies by identifying selective slowing of conduction in median nerve fibers across the carpal tunnel. Nerve ultrasound may be helpful in identifying nerve trunk enlargement.

Carpal tunnel syndrome may improve with a change in activity and the nocturnal use of wrist splints. Decompression by section of the transverse carpal ligament is the only curative procedure. Since diabetes delays nerve regeneration, recovery in diabetics, particularly those poorly controlled, may be less robust than in nondiabetics.

ULNAR NEUROPATHY AT THE ELBOW

Ulnar neuropathy at the elbow presents with pain and sensory symptoms in the medial half of the ring finger and in the fifth digit, sometimes radiating into the palm as far proximally as the wrist. Sensory loss involves these fingers as well as the medial volar and dorsal hand to the wrist. There may be wasting and weakness of intrinsic ulnar-innervated hand muscles, especially the first dorsal interosseous muscle, making it difficult for the patient to abduct or adduct the fingers. Manipulation of the ulnar nerve at the elbow may generate tingling that radiates into the hand and reproduces symptoms. Ethanol use and previous elbow trauma or fractures are predisposing factors. The disorder is commonly caused by the patient leaning on the medial elbow, compressing the nerve. The prevalence of ulnar nerve entrapment in patients with diabetes mellitus is estimated to be approximately 2 percent.[9]

Electrophysiologic studies identify slowing of ulnar motor and sensory conduction across the elbow, loss of ulnar SNAPs and CMAPs, and sometimes conduction block across the elbow. EMG demonstrates evidence of denervation in weak muscles. Changes in elbow position or protecting the nerve with padding can reverse the neuropathy. There are no controlled clinical trials specifically in diabetic patients to show that surgical decompression improves long-term outcome. However, current clinical practice suggests decompression is a reasonable approach when the lesion is symptomatic, involves motor axons, and is progressive despite conservative measures.

MERALGIA PARESTHETICA

Meralgia paresthetica is an entrapment neuropathy involving the lateral femoral cutaneous nerve of the thigh as it passes under the inguinal ligament. Symptoms are numbness, tingling, prickling, and sometimes pain over the lateral thigh that may be relieved by sitting. Bilateral involvement may occur. Examination findings include loss of sensation to light touch and pinprick over the lateral thigh. The extent of findings may vary from a small patch to most of the lateral thigh from just below the inguinal area to the knee. Hip flexion and knee extension muscle power is preserved, as is the quadriceps stretch reflex. In some patients, a compressive lesion such as an enlarged lymph node, inguinal hernia, or scar from a previous hernia repair is present. Additional risk factors are abdominal obesity, pregnancy, and the wearing of low-riding belts. The differential diagnosis includes diabetic lumbosacral plexopathy (distinguished by weakness and wasting along with loss of the quadriceps reflex), plexopathy secondary to a retroperitoneal lesion, or an L3 or L4 radiculopathy associated with back pain, weakness, positive straight leg raising sign, and loss of the quadriceps reflex. There is no evidence to support benefit from surgical decompression at the inguinal ligament; however, some patients may choose to undergo decompression if weight loss, local anesthetic, or corticosteroid injections are unhelpful and pain is intractable. Conservative management of pain and limiting activities that provoke symptoms may allow spontaneous recovery over time.

INTERCOSTAL OR TRUNCAL RADICULAR NEUROPATHIES

Intercostal neuropathies involve the thorax and abdominal wall and may be ischemic in origin. Patients may present with severe thoracic or abdominal wall pain mistaken for an intra-abdominal or thoracic emergency. Differential diagnoses include herpes zoster without rash or radiculopathy from a segmental structural lesion. Several contiguous territories may be involved unilaterally or bilaterally.[10] Symptoms other than pain include tingling, pricking, lancinating, aching (especially at night), radiation around the chest or abdomen causing a feeling of constriction, and allodynia. Patients may occasionally have asymptomatic sensory loss over the chest or abdomen from longstanding truncal or radicular neuropathy or asymmetric weakness of the abdominal muscles when sitting up (asymmetric bulging). Men are affected more often than women. Imaging of the spinal cord and roots by magnetic resonance imaging (MRI) with gadolinium should be performed to exclude nerve root compression when a structural lesion is suspected. In some patients, EMG may detect signs of denervation in weak thoracic intercostal or abdominal muscles; such changes commonly are more extensive and may involve the paraspinal muscles at multiple levels. Pain may be severe enough to require treatment, but usually reaches a maximum after several weeks, continues for some months, and then gradually resolves completely. Sensory loss may also slowly resolve with time.

OCULOMOTOR NEUROPATHY

Oculomotor neuropathy develops in older diabetic patients, particularly if they are also hypertensive. Symptoms consist of sudden-onset diplopia and ptosis, with an aching pain around or behind the eye. The eye is deviated laterally. Diabetic oculomotor palsy typically spares the pupil because axons within the center of the nerve are targeted rather than peripheral pupillomotor fibers. This centrofascicular involvement in diabetes suggests that the pathology is ischemic nerve damage. A single pathologic study of a patient with oculomotor palsy noted demyelination in the center of the oculomotor nerve within the cavernous sinus.[11] Imaging should include MRI of the brainstem and the course of the oculomotor nerve; MR angiography is indicated to search for an aneurysm compressing the third cranial nerve. CT angiography may also be used to exclude aneurysm but there is a risk of contrast nephropathy from the contrast load. Although no specific treatment is available for the neuropathy, spontaneous resolution usually occurs over approximately 3 months. An eye patch prevents diplopia but interrupts binocular depth vision and patients should therefore refrain from driving.

DIABETIC LUMBOSACRAL PLEXOPATHY

Diabetic lumbosacral plexopathy (also known as radiculoplexus neuropathy, diabetic amyotrophy, Bruns–Garland syndrome, and proximal diabetic neuropathy) usually develops in patients with type 2 diabetes mellitus, especially in men. It may emerge early in the course of diabetes or following onset of insulin therapy. Nondiabetics rarely can develop a similar syndrome. Symptoms are severe and disabling with impairment in standing and walking. The subacute onset of unilateral intense deep boring or aching muscle pain is typical, sometimes worse at night, located within the muscles of the thigh but also often radiating to the back and perineum. These symptoms are followed by weakness and wasting of the proximal thigh muscles including the quadriceps, iliopsoas, hip adductor muscles, and occasionally the anterior tibial muscles (with associated foot drop). Sensory loss and tingling are less prominent. The condition can be distinguished from a femoral neuropathy by the pattern of muscle involvement, which typically includes the medial adductor muscles innervated by the obturator nerve, and the iliopsoas muscle innervated directly by the lumbar plexus. Over the months, slow recovery of muscle power occurs. In some patients, contralateral symptoms may emerge a few weeks after onset.

Variations of diabetic lumbosacral plexopathy include symmetric involvement, more prominent foot drop, or apparent worsening of polyneuropathy. The pathophysiologic mechanism for this form of focal neuropathy is uncertain but may include occlusive changes in microvessels supplying the lumbosacral roots or plexus or inflammatory changes suggestive of a localized form of vasculitis. Perivascular inflammation, epineurial inflammation, microvessel occlusion, and iron deposition (indicative of intraneural bleeding) accompany loss of axons in biopsies of the sural nerve or cutaneous nerves of the thigh.[12]

Imaging studies of the lumbar intraspinal space (MR with gadolinium) and the lumbosacral plexus (MR with gadolinium or CT with contrast) help to exclude a retroperitoneal compressive plexus lesion. Electrophysiologic studies in diabetic lumbosacral plexopathy show loss of amplitude of the CMAP recorded over the quadriceps muscle and EMG evidence of denervation in weak muscles.

No therapy has been shown to arrest or reverse the motor deficit. Despite the inflammatory changes seen on pathologic examination, the response to immunosuppressive therapy is unproven. Patients require intensive pain management. Physiotherapy and occupational therapy are essential to recovery and a knee brace helps to prevent buckling when weight bearing.

OTHER FOCAL NEUROPATHIES

Other focal neuropathies described in diabetic patients are less common. Bell palsy, presenting with unilateral facial weakness, may be more common in diabetics. Abducens palsy presents with lateral gaze weakness of the abducting eye and is seen in older diabetic patients; other causes include compression, trauma, and hypertension. Trochlear palsy presents with diplopia and difficulty looking down and inward because of weakness of the superior oblique muscle.

The patient tilts the head to the side opposite the palsy to reduce diplopia.

Autonomic Neuropathy

Autonomic neuropathy in diabetes may target one or more components of the autonomic nervous system.

Cardiovascular abnormalities include loss of reflexes such as heart-rate variability in various circumstances including at rest, with the Valsalva maneuver, and following standing. In severe disease, patients may have a fixed, mildly elevated heart rate that resembles a transplanted heart without innervation. More commonly, partial denervation of the heart may contribute to abnormal contractility and arrhythmias. For example, prolonged QTc intervals in patients with type 1 diabetes may predict an increased risk of mortality. Postural hypotension, from loss of sympathetic control of resistance arterioles, is defined as a decline of systolic pressure by 20 mmHg or more—or of diastolic pressure by at least 10 mmHg—after 1 minute of standing, with associated orthostatic dizziness or fainting; it occurs in 3 to 6 percent of diabetics and may be a late feature of diabetic autonomic neuropathy. Some patients may also have abnormal tachycardia with standing (postural orthostatic tachycardia syndrome), as discussed in Chapter 8.

Treatment includes stopping or reducing medications that may cause postural hypotension (e.g., tricyclic antidepressants, antihypertensive medications, and other vasodilators); arising from a bed or chair slowly; sleeping with the head of the bed raised 20 degrees; avoiding prolonged standing; avoiding early morning or postprandial exercise; avoiding prolonged heat exposure, hot baths or showers; increasing salt and fluid intake; and limiting alcohol intake. Medications used to treat postural hypotension include fludrocortisone, midodrine, L-dihydroxyphenylserine (Droxidopa), and desmopressin (see Chapter 8).

The Ewing battery is a set of cardiovascular autonomic tests that includes heart-rate response to the Valsalva maneuver, standing, and to deep breathing, as well as blood-pressure response to standing up and sustained handgrip. Radioiodinated metaiodobenzylguanidine (MIBG) is an injectable marker of sympathetic terminals found in cardiac muscle; loss of MIBG uptake in the inferior, posterior, and apical portions of the heart occurs in diabetes, indicating sympathetic denervation or dysfunction.

Sexual dysfunction is common in diabetic men. ED, defined as the inability to achieve or maintain an erection sufficient for sexual intercourse, may occur in over 40 percent. Direct vascular factors, such as atherosclerosis, also cause ED but other causes should be excluded including psychologic factors, Peyronie disease, problems with the sexual partner, and medications (e.g., sedatives, antidepressants, and antihypertensives). The additional loss of ejaculation suggests more severe autonomic involvement. Testing includes duplex ultrasonography and nocturnal measurements of penile tumescence. Treatment for male ED involves phosphodiesterase-5 inhibitors (sildenafil, tadalafil, others), apomorphine, intracavernosal and intraurethral therapy, vacuum devices, and penile prostheses, as discussed in Chapter 30. Female sexual dysfunction may also occur from vaginitis, loss of vaginal lubrication, cystitis, and other causes.

Gastrointestinal neuropathy is associated with abdominal pain, weight loss, early satiety, postprandial fullness, heartburn, nausea (rarely vomiting), dysphagia, fecal incontinence, diarrhea (which may be nocturnal), and constipation. Esophageal transit and gastric emptying are slowed, a change directly linked to elevated glucose levels. Similarly, small intestine dysmotility develops and may accompany an increased risk of cholelithiasis and cholecystitis. Colonic dysfunction causes constipation and diarrhea that may be alternating and may be associated with abdominal pain. Anorectal dysfunction with incontinence develops from abnormal internal or external sphincter function, loss of sensitivity, and disrupted anorectal reflexes. A superimposed history of obstetric trauma may predispose diabetic women to this complication. Exclusion of other gastrointestinal problems that can occur in patients with diabetes is important, including esophageal candidiasis, gastric bezoar, *Helicobacter pylori* infection, bacterial overgrowth, anorectal disorders, celiac disease, hemorrhoids, impaired sphincter tone, rectal prolapse, local tumors, ulcers, rectal intussusception, and fecal impaction.

Gastric and intestinal motility studies are performed using radiography or scintigraphy, manometry, pH recordings, and endoscopy or colonoscopy. Anorectal dysfunction is studied by manometry, ultrasonography, proctoscopy, and sigmoidoscopy. High-fiber, low-fat diets may facilitate gastric emptying. Pharmacologic treatments of slowed gastric emptying include prokinetic agents (e.g., domperidone, metoclopramide, erythromycin). Cisapride has been withdrawn from the market in many countries because of an increased risk of cardiac arrhythmia and death. For intractable impaired gastric emptying, a temporary or permanent jejunostomy may rarely be required. For diarrhea, opioids (e.g., loperamide, codeine), cholestyramine, fiber, and bulking agents may be useful. Biofeedback may help with fecal incontinence.

Bladder neuropathy leads to loss of bladder sensitivity and later detrusor muscle weakness, both of which contribute to incomplete bladder emptying, recurrent infection, and eventual overflow incontinence (see Chapter 29). In late disease, an end-stage insensitive noncontractile atonic bladder can result. Symptoms of bladder neuropathy include urgency, nocturia, and incontinence. Other urologic problems such as bladder tumor, infection, urethral stricture, or prostatic hypertrophy should be excluded. Urodynamic studies may be helpful, including urinary tract imaging (e.g., intravenous pyelography), cystography, uroflowmetry, and post-void ultrasonography to test for residual urine. Pharmacotherapy may include parasympathomimetics and α-adrenergic blockade to relieve sphincter hypertonicity. End-stage dysfunction may require intermittent self-catheterization.

Sudomotor neuropathy, or abnormalities of sweating, can cause stocking-and-glove distribution anhidrosis, a risk factor for skin ulceration in the feet. Generalized loss of sweating increases heat intolerance. Diabetic subjects may have abnormal sweating patterns such as inappropriate truncal sweating, or gustatory sweating (facial and truncal sweating induced by eating certain foods). Thermoregulatory sweat testing examines the geographic distribution of sweating. Quantitative sudomotor axon reflex testing (QSART) tests quantitative sweat output using a dehumidified sweat capsule; in diabetes, output may be reduced, absent, excessive, or "hung up" (persistent). The sympathetic skin response is an electrophysiologic surrogate for sweat gland activation. Other measures of sweat output include analysis of sweat droplet numbers (numbers of functioning sweat glands) and size; skin biopsy to analyze sweat gland innervation; and novel rapid sweat indicator methods available commercially. For patients with hypohidrosis or anhidrosis, caution regarding heat exposure should be advised. Moisturizers may be applied to dry feet and hands.

Autonomic neuropathy may cause small pupils with sluggish or absent pupillary reflexes accompanied by light intolerance. Pupils may be examined by pupillography to measure pupillary diameter, latency to contraction, and velocity of contraction and dilatation.

Patients with diabetes may have hypoglycemic unawareness because autonomic responses (e.g., sweating, tachycardia) and counter-regulatory hormones such as epinephrine fail to increase. Patients may not recognize their impairment and thus fail to take adequate protective measures.

CENTRAL NERVOUS SYSTEM COMPLICATIONS

Cognitive Dysfunction

A complication of diabetes mellitus that is frequently overlooked or under-reported is cognitive decline.[13] An association between diabetes mellitus and cognitive dysfunction was first described almost a century ago, and occurs with either type 1 or type 2 diabetes. Both have an elevated risk of dementia, cerebral atrophy, and the presence of white matter abnormalities. The impact may be most apparent during childhood or in late stages of life when neurodegeneration may predominate. For example, diabetic patients have an increased risk of development of Alzheimer disease (AD) as compared with nondiabetic subjects, possibly predated by early blood–brain barrier changes. Many AD patients also have glucose intolerance.

Children with type 1 diabetes have lower intelligence scores, lowered mental efficiency, and poor school performances when compared to classmates without diabetes. The younger the age of onset of the diabetes, the greater the cognitive impact. The exact role of hypoglycemic episodes is unclear. While some reports have speculated on the association between lifetime hypoglycemic episodes and cognitive impairment, more recent studies have not demonstrated such an association even though hypoglycemic events are known to cause hippocampal damage. Chronic hyperglycemia may accelerate neurodegeneration. Hyperglycemia in children with type 1 diabetes has also been shown to lead to altered white matter development.

In type 2 diabetes mellitus, there are several confounding factors that may influence cognition, such as obesity, dyslipidemia, hypertension, and stroke. Patients with prediabetes or impaired glucose tolerance may also have cognitive impairment, but to a lesser degree. An important comorbidity is depression, which may lead to synergistic effects on executive function.

Some domains of cognition are impacted more than others in diabetes—these include changes in attention, executive function, visual and verbal memory, processing speed, mental flexibility, and planning. In contrast, language and visuospatial construction ability do not appear to be compromised. Motor impairment, less commonly studied and confounded by the impact of polyneuropathy, appears to be linked to cognitive decline.

Changes present in the diabetic brain over time can be described pathologically as a diabetic leukoencephalopathy, characterized by cerebral atrophy, cognitive decline, and white matter abnormalities (Fig. 19-3).

Studies examining cognitive function in diabetics require additional factors to be considered, including glycemic control, duration of diabetes, and specific treatments used. It is well known that longer durations of diabetes and poor glycemic control are associated with greater microvascular end-organ complications in both type 1 and type 2 diabetes. An elevated HbA1c level, indicating more significant chronic hyperglycemia, is also associated with greater severity of impaired cognition in patients with type 2 diabetes. It is possible that cognitive dysfunction is partially reversible with improvements in glycemic control, although optimal target levels have not yet been established.

Cerebral Infarction and Vascular Dementia

Diabetes mellitus is a prominent risk factor for atherosclerosis and cerebral infarction. Diabetes is usually associated with lacunar infarction involving small penetrating arteries in addition to large-vessel infarction. As a result, patients with multi-infarct (or vascular) dementia have a greater prevalence of

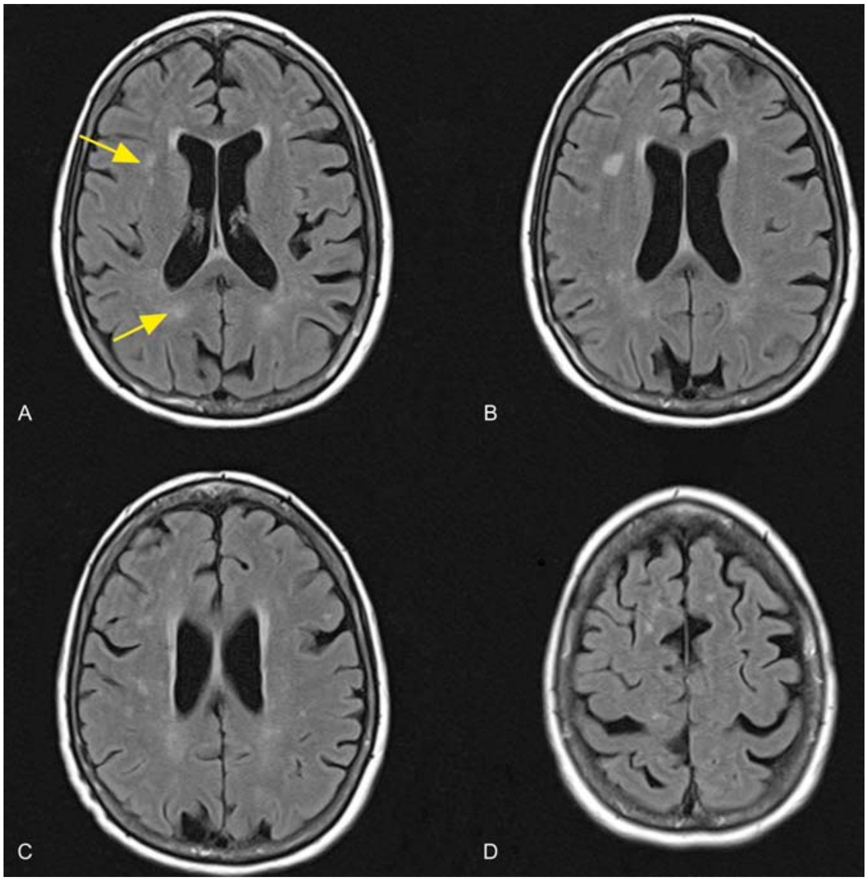

FIGURE 19-3 ■ Magnetic resonance imaging of the brain from a 62-year-old woman with type 2 diabetes mellitus for 12 years, who presented with mild ataxia of gait and polyneuropathy. These axial T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences progress from caudal to rostral cuts, *A* to *D*, and show nonenhancing bilateral white matter hyperintensities (*arrows*) in *A*, also termed diabetic leukoencephalopathy.

diabetes than other patients with dementia. Vascular dementia is the second most common worldwide cause of dementia following AD, and both are rising in prevalence.

Alzheimer Disease

There has also been a longstanding association between diabetes and vascular dementia in longitudinal population-based studies, but the relationship between diabetes and AD has been recognized more recently. Depending upon the country, gender, and ethnicity of the population considered, AD generally comprises 50 to 70 percent of all causes of dementia. Reduced glucose tolerance, insulin resistance, and hyperinsulinemia are negatively correlated with memory and are associated with hippocampal atrophy. Diabetes is associated with neuropathologic markers of AD, including β-amyloid and tau accumulation.

Insulin resistance is related to an increased risk for cognitive decline and linked with a reduction in cerebral glucose metabolic rates and more subtle cognitive impairment. The major gene linked with AD, the apolipoprotein E gene (particularly the ε4 allelic variant) is associated with a greater atherosclerotic risk profile and higher risks of both vascular dementia and AD in patients with diabetes. Hyperinsulinemia's impact upon the brain includes downregulation of insulin-signaling pathways, including the degrading enzyme insulysin. Insulin inactivates glycogen synthase kinase 3 (GSK-3) through phosphoinositide (PI) 3-kinase (PI3K), subsequent Akt (also called protein kinase B) activation, and then Akt-mediated phosphorylation of GSK-3 isoforms, ultimately inhibiting GSK-3 activity. As such, insulin regulates tau protein phosphorylation. Insulin-mediated GSK-3 inhibition may therefore prevent tau protein hyperphosphorylation or reduce Aβ protein accumulation. Hyperinsulinemia or insulin resistance also promotes amyloidosis. As such, peripheral insulin increases measurable Aβ levels in CSF, potentially accelerating AD. Finally, insulin signaling influences neuronal senescence and life span; reduced hippocampal synaptic plasticity occurs both with peripheral and CNS insulin resistance and may be linked to hippocampal atrophy.

Pathogenic synergy exists with diabetic leukoencephalopathy and AD, in apolipoprotein processing and disruption of insulin signaling. The advanced glycation end-product (AGE) pathway[14] renders additional toxicity associated with greater oxidative stress and reduced nitric oxide bioavailability. AGEs propagate with hyperglycemia in diabetes as well as during aging, corresponding with an upregulation of the receptor for AGEs, called RAGE—a ubiquitous multiligand transmembrane receptor of the immunoglobulin superfamily of cell surface molecules. AGE-RAGE signaling initiates protein kinase pathways including proinflammatory gene activation and secondary immune responses including rises in NFκB, a stress responder.

NEUROPATHIC PAIN

Neuropathic pain can develop in the setting of diabetic polyneuropathy or mononeuropathies and may occur at any stage of these disorders. In diabetic polyneuropathy, neuropathic pain is typically described as nocturnal burning discomfort, allodynia, electric-like jolts, or a deep aching pain.

Pathophysiology

Altered excitability of axons, associated with early molecular alterations of both peripheral axons and the cell bodies of neurons in sensory ganglia, explains why patients may have prominent neuropathic pain despite only mild loss of nerve fibers. Changes in the distributions of sodium or calcium channels that promote abnormal ectopic discharges may initiate the pain cascade. Specific channels include upregulated $Ca_v3.2$ T-type calcium channels and sodium channels ($Na_v1.3$, $Na_v1.9$, and $Na_v1.7$). Other molecules involved in neuropathic pain may include bradykinin B1 receptors (BKB1-R), VR1 (vanilloid, TRPV1) receptors, TRPA1 (transient receptor potential cation channel, subfamily A, member 1), protein kinase C (PKC), and COX-2. Finally, changes at the level of the dorsal horn of the spinal cord or higher may also be implicated in the development of neuropathic pain. Overall, work by a number of investigators suggests that diabetic polyneuropathy is associated with multilevel changes in the neuraxis that promote pain, including alterations of primary sensory neurons and abnormal signaling through the dorsal horn of the spinal cord.

Treatment

The current state of the literature evaluating analgesic therapy for human diabetic polyneuropathy has been reviewed elsewhere.[15] There is evidence supporting the use of tricyclic antidepressants, gabapentin, pregabalin, duloxetine, and tramadol. However, opioids are no longer recommended for nonmalignant neuropathic pain. Gabapentin is excreted renally and thus downward dose revision is necessary in patients with renal failure.

Treatment guidelines have been published by the American Academy of Neurology, in association with other professional organizations and based on Class I evidence. Pregabalin was determined to lessen the pain of peripheral diabetic neuropathy and improve quality of life and sleep (recommendation level A). Gabapentin and sodium valproate were classified as probably effective and given a level B recommendation. A flag concerning the risk of birth defects was placed for sodium valproate. Other agents deemed probably effective (level B) were amitriptyline, venlafaxine, duloxetine, dextromethorphan, morphine sulfate, tramadol, oxycodone, capsaicin, isorbide dinitrate, and percutaneous electrical stimulation. Topiramate, desipramine, imipramine, fluoxetine, alpha lipoic acid, or the combination of nortriptyline and fluphenazine had insufficient evidence for or against their use. Oxcarbazepine, lamotrigine, lacosamide, clonidine, pentoxifylline, and mexiletine had evidence against their effectiveness (negative level B recommendation). Other guidelines have provided similar recommendations. More studies on the effectiveness of synthetic and naturally occurring cannabinoids is required before any concrete conclusions can be made.

SPECIFIC THERAPEUTIC AGENTS

Calcium channel $\alpha 2$-δ ligands include gabapentin and pregabalin. Gabapentin is initiated in low doses such as 300 mg at bedtime and increased to a maximum of 3,600 mg daily. It does not alter the metabolism of other drugs, but dose reduction is required in renal failure. Side effects include dizziness, fatigue, and cognitive dysfunction with initial use or higher doses, and lower limb edema. Pregabalin is started at 75 mg at bedtime, and titrated upwards using a twice-daily dosing schedule to a maximum of 600 mg daily; its side effects are similar to those of gabapentin.

Serotonin and norepinephrine reuptake inhibitors include venlafaxine, which is initiated at 37.5 mg per day and increased weekly to a maximum of 225 mg daily. Side effects include nausea, dizziness, drowsiness, hyperhidrosis, hypertension, and constipation. Duloxetine is started at 30 mg daily titrated up to a maximum of 120 mg daily, although 60 mg daily provides optimal outcomes. Adverse effects include hepatotoxicity, nausea, dry mouth, constipation, somnolence, hyperhidrosis, and decreased appetite. Amitriptyline is started at 10 to 25 mg at bedtime and increased to 100 to 150 mg. Side effects include next-day drowsiness, lethargy, dry mouth, constipation, and urinary retention. Amitriptyline may help with prominent nocturnal pain but requires caution in patients with cardiac disease or urinary retention.

Agents to treat local pain include lidocaine patches, other local anesthesia agents and capsacin. Some patients find these to be acceptable alternatives to oral medications.

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CHAPTER

20

Sex Hormone, Pituitary, Parathyroid, and Adrenal Disorders and the Nervous System

HYMAN M. SCHIPPER ■ GARY M. ABRAMS

SEX HORMONES AND THE NERVOUS SYSTEM
- Migraine
- Stroke
- Epilepsy
- Movement Disorders
  - *Chorea*
  - *Parkinsonism*
  - *Wilson Disease*
  - *Other Movement Disorders*
- Nervous System Neoplasms
  - *Meningiomas*
  - *Gliomas*
  - *Other Tumors*
- Multiple Sclerosis
- Alzheimer Disease
- Neuropsychiatric Disorders
  - *The Porphyrias*
  - *Premenstrual Syndrome*
  - *Depression and Psychosis*
- Sleep Disorders
- Intracranial Hypertension
- Neuromuscular Diseases
  - *Catamenial Sciatica*
  - *Other Neuromuscular Disorders*

PITUITARY GLAND
- Sellar and Parasellar Lesions
- Anterior Pituitary
  - *Prolactin*
  - *Growth Hormone*
  - *Adrenocorticotropic Hormone and Cushing Disease*
  - *Thyroid-Stimulating Hormone*
  - *Clinically Nonfunctioning Pituitary Adenomas*
  - *Pituitary Apoplexy*
- Posterior Pituitary
  - *Diabetes Insipidus*
  - *Syndrome of Inappropriate Antidiuretic Hormone Secretion*
- Hypopituitarism

PARATHYROID GLANDS
- Primary Hyperparathyroidism
- Hypoparathyroidism

ADRENAL GLANDS
- Adrenal Cortex
  - *Primary Aldosteronism*
  - *Cushing Syndrome*
  - *Adrenal Insufficiency*
- Adrenal Medulla
  - *Pheochromocytoma and Neuroendocrine Tumors*

The most common endocrine disorders causing neurologic disease are thyroid disease and diabetes mellitus, which are addressed in Chapters 18 and 19. Nevertheless, sex hormone, pituitary, parathyroid, and adrenal disorders may have important neurologic implications or consequences and are therefore reviewed here, with emphasis on features relevant to neurologic practice.

SEX HORMONES AND THE NERVOUS SYSTEM

The effects of sex steroids on neurologic function in health and disease constitute a rich and rapidly expanding area of basic and clinical neuroscience. Sex steroids exert both organizational and activational effects within the nervous system. Organizational

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effects refer to the irreversible differentiation of neural circuitry resulting from exposure to sex steroids during critical periods of brain development and are discussed in the previous edition of this book. The activational effects of sex steroids encompass a myriad of largely reversible neurophysiologic influences exerted by gonadal hormones on the mature nervous system. Such interactions are essential for regulation of the brain–pituitary–gonadal axis (Fig. 20-1) and the establishment of normal patterns of sexual, aggressive, cognitive, and autonomic behaviors. Furthermore, by impacting neurosteroidogenesis and the metabolism and release of various central neurotransmitters and neuromodulators, hormonal fluctuations associated with (1) specific phases of the menstrual cycle, (2) pregnancy, (3) the menopause, and (4) exposure to exogenous sex hormones may induce or modify a host of neurologic and neuropsychiatric disorders.

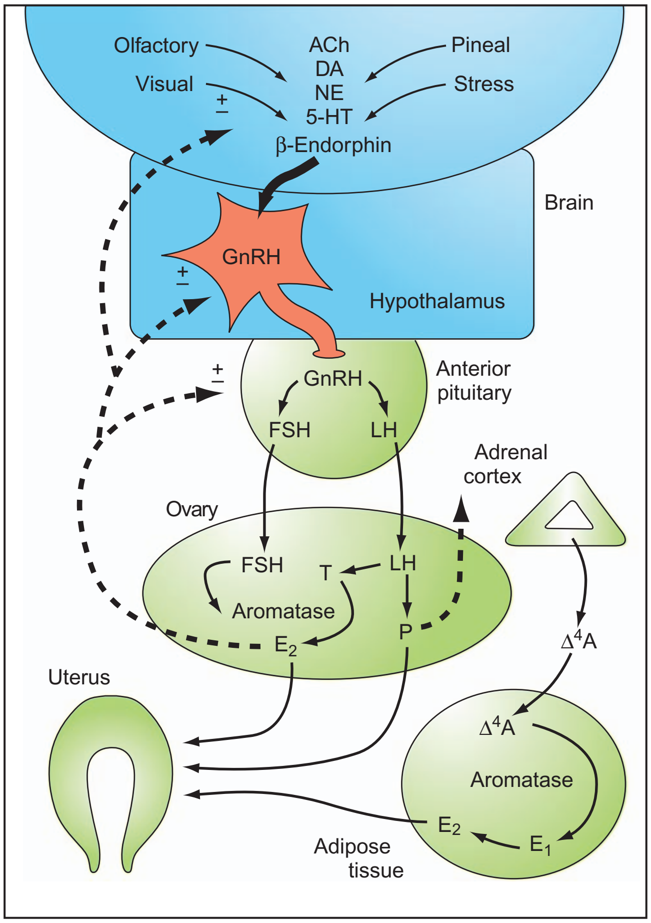

FIGURE 20-1 ■ The brain–pituitary–ovarian axis. Δ^4A, delta-4-androstenedione; ACh, acetylcholine; DA, dopamine; E_1, estrone; E_2, estradiol; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; 5-HT, 5-hydroxytryptamine (serotonin); LH, luteinizing hormone; NE, norepinephrine; P, progesterone; T, testosterone.

Migraine

Although no gender difference in its prevalence is apparent before puberty, migraine is three times as common in adult women (18%) as in men (6%).[1,2] Approximately 60 percent of women with migraine experience perimenstrual exacerbations of their headaches (catamenial migraine). The late luteal-phase decline in plasma estradiol (but not progesterone) appears to play an important role in the precipitation of catamenial migraine. The frequency or severity (or both) of migraine attacks often diminishes with gestation, particularly in patients whose headaches are linked to the menstrual cycle. The absence of rhythmic estrogen "withdrawal" characteristic of the pregnant state is believed to be responsible for the reduction in migraine activity. Indeed, many women whose headaches are attenuated by pregnancy experience relapses at the time of parturition, when sex hormone levels fall precipitously. In some women, breastfeeding appears to protect against migraine recurrence. Occasionally, migraine arises for the first time or appears to worsen during gestation or the perimenopausal period. A first approach to the management of gestational migraine should be nonpharmacologic (e.g., relaxation training, biofeedback), especially during the first trimester when risks of teratogenicity and embryotoxicity are greatest. For severe attacks, acetaminophen with codeine or nonsteroidal anti-inflammatory drugs (NSAIDs) may have to be used. Further discussion is provided in Chapters 31 and 59. For status migrainosus in pregnancy, chlorpromazine, meperidine, morphine, or prednisone may need to be administered. Perimenopausal migraine often responds to standard estrogen replacement therapy, but this must be weighed against the risk of developing breast cancer in individual patients. Fluoxetine and venlafaxine may be beneficial in women with perimenopausal migraine and comorbid hot flashes.

An association between migraine and oral contraceptives is frequently encountered in clinical practice. Women often exhibit new onset or exacerbation of migraine while taking oral contraceptives. Attacks tend to manifest during the first few cycles (particularly on placebo days in accord with the estrogen withdrawal hypothesis) and usually, but not invariably, resolve on discontinuation of the medication. A qualitative change in the pattern of migraine is noted in some patients. For example, a migraineur may develop a focal prodrome for the first time while taking oral contraceptives. Women in this category may be at high risk of infarction in regions reflecting the distribution of their auras. Amelioration of migraine after exposure to oral contraceptives is sometimes observed, perhaps related at least in part to psychologic factors.

The pathophysiology of estrogen-related migraine is incompletely understood. Estrogens may act directly on vascular smooth muscle as well as modulate the activity of vasoactive substances at the neurovascular junction. In addition, by altering central prostaglandin, serotonin, opioid, prolactin, or calcitonin gene-related peptide metabolism, premenstrual changes in circulating estrogens may activate vasoregulatory elements in the brainstem or hypothalamus, which, in turn, may trigger symptomatic alterations in cerebrovascular tone.

First-line therapy for menstrual migraine should include the standard pharmacologic, dietary, and psychologic modalities employed in the general migraine population. Sumatriptan and related serotonin 5-HT_{1D} (presynaptic autoinhibitory) receptor agonists are equally effective for noncatamenial and menstrual migraine. Refractory cases of severe catamenial migraine may benefit from late luteal-phase therapy with prostaglandin inhibitors (e.g., naproxen, 250 to 500 mg orally twice daily) and mild diuretics. Hormonal interventions in catamenial migraine have been largely unsuccessful and are often complicated by unpleasant side effects. Oral contraceptives usually exacerbate migraine and probably should not be used in the treatment of this disorder. The use of estrogen implants has yielded contradictory results. The risk–benefit ratio accruing to long-term estrogen therapy must be carefully assessed before such treatment can be advocated for this relatively benign condition. The antiestrogen tamoxifen may either alleviate or precipitate catamenial migraine. The beneficial effect of tamoxifen may be due to inhibition of calcium uptake or prostaglandin E synthesis in these subjects. In several reports, danazol (200 mg twice daily for 25 days), a testosterone derivative used in the management of endometriosis, aborted or ameliorated premenstrual migraine for the duration of treatment; catamenial headaches resumed on its discontinuation. Continuous bromocriptine therapy (2.5 mg three times daily) results in a substantial decline of headache frequency in menstrual migraine. In addition to migraine, menstruation, pregnancy, and menopause may also influence cluster headache, other autonomic cephalalgias, and hemicrania continua.

Stroke

Oral contraceptives have been implicated as a significant risk factor in thromboembolic cerebral infarction, subarachnoid hemorrhage, and cerebral venous thrombosis.[2] In the late 1960s, case-control studies revealed a 6- to 19-fold increased risk of ischemic stroke in young women related to the use of oral contraceptives. Hypertension, migraine, and age older than 35 years are associated, but independent, risk factors for cerebral infarction in patients taking oral contraceptives. Cigarette smoking by women on oral contraceptives was found to increase further the likelihood of hemorrhagic but not thromboembolic stroke. Ingestion of lower-dose (30 μg) estrogen preparations appears to be responsible for a decline in rates of thromboembolic disease among users of oral contraceptives. In a population-based case-control study, the odds ratio of ischemic stroke in current users of low-dose estrogen contraceptives (20 to 35 μg) was only slightly higher compared with former users or women who were never exposed to oral contraceptives. However, the risk of stroke remains unacceptably high in low-dose oral contraceptive users if they smoke and are older than the age of 35. Recent evidence suggests that exposure to ultralow-dose oral contraceptives (containing <25 μg ethinyl estradiol) may not enhance stroke risk when used in normotensive nonsmokers. Although less often implicated than estrogens, progestins may contribute to the danger of cerebral infarction by promoting hypertension, hypercoagulability, and adverse serum lipoprotein levels.

Ischemic strokes in users of oral contraceptives have been localized to the carotid (usually the middle cerebral artery or its deep penetrating branches) and vertebrobasilar distributions. There is usually no radiologic or pathologic evidence of disseminated vascular disease in young women with oral contraceptive-related stroke. Cerebral thromboembolism resulting from estrogen-induced hypercoagulability is a likely etiology for such strokes. Estrogen increases plasma levels of fibrinogen and clotting factors VII, VIII, IX, X, and

XII. The steroid also enhances platelet aggregation and suppresses antithrombin III activity and the fibrinolytic system. A host of estrogen-regulated genes may impact the risk of ischemic stroke, either positively or negatively. Certain inherited prothrombotic conditions (e.g., G20210A prothrombin, factor V Leiden, or methylenetetrahydrofolate reductase C677T polymorphism) augment the risk of ischemic stroke substantially if present in oral contraceptive users. Sex hormone-induced hypercoagulability is thought to play an important role in the pathogenesis of cerebral venous thrombosis complicating pregnancy, the puerperium, and use of hormonal contraceptives.

Increased levels of endogenous free estradiol may be an indicator of atherothrombotic stroke risk in older postmenopausal women, particularly in those with greater central adiposity. Dyslipidemia, insulin resistance, inflammation, and several adipose-derived hormones (e.g., adiponectin, leptin, ghrelin) are potential mediators of this association. On the other hand, estrogens may mitigate atherosclerotic vascular disease by inhibiting NFκB signaling in macrophages and the production of proinflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor (TNF)-α.[2] Data concerning the impact of hormone replacement therapy (HRT) on stroke incidence and severity are conflicting, with reports of neutral, increased, and decreased stroke risk accruing from this intervention. In some observational studies, HRT-related stroke risk was significantly modified by the presence or absence of associated factors such as hypertension or smoking. Importantly, several large randomized controlled studies indicated that HRT with conjugated equine estrogen or 17β-estradiol, alone or combined with medroxyprogesterone acetate, does not protect against stroke (or coronary artery disease) in women with established vascular disease and may actually worsen outcomes in this high-risk population. In healthy women without prior cerebrovascular history, an increased risk of ischemic but not fatal or hemorrhagic stroke has been attributed to 17β-estradiol replacement therapy. The risk of ischemic stroke in women receiving HRT does not appear to be modified by age of hormone initiation or by temporal proximity to menopause.

HRT with transdermal low-dose estrogens alone or combined with micronized progesterone may be particularly favorable in minimizing risk of ischemic stroke. Interestingly, men with the common ESR1 c.454−397CC variant of the estrogen receptor-alpha (*ESR*a) gene may be more prone to ischemic stroke than men bearing other *ESR*a genotypes after adjusting for age, hypertension, diabetes, blood lipid levels, and smoking status.

The relative risks of subarachnoid hemorrhage in former users and current users of moderate- to high-dose oral contraceptives were four times those of the general population. The odds ratio for hemorrhagic stroke in current users of low-dose estrogen contraceptives (20 to 35 μg) in comparison with former users or nonusers is negligible. As in the case of ischemic stroke, cigarette smoking and age older than 35 years substantially increase the risk of subarachnoid hemorrhage in users of oral contraceptives. Female sex hormones may predispose to bleeding from both aneurysms and arteriovenous malformations, although the pathophysiologic mechanisms underlying these phenomena remain controversial. By analogy to their effects on endometrial spiral arteries, fluctuating sex hormone levels may compromise the integrity of cerebral arterial walls, rendering them more susceptible to rupture. During pregnancy, hemodynamic changes may facilitate engorgement and bleeding from cerebral arteriovenous malformations. In addition, sex hormones may exert direct trophic influences on these malformations, analogous to their effects on other highly vascularized lesions such as spider angiomas, gingival epulis, and meningiomas (discussed later). Rarely, subarachnoid hemorrhage is secondary to cyclic bleeding from hormone-sensitive ectopic endometriomas of the spinal canal.

Epilepsy

Normal reproductive processes may be disrupted by seizure disorders and their therapies. Abnormal limbic discharges may be responsible for the hyposexuality and increased prevalence of hypogonadotropic hypogonadism and polycystic ovary syndrome noted in patients with temporal lobe epilepsy.

As discussed in Chapter 31, anticonvulsant therapy in women of childbearing age may result in failure of oral contraceptives and in teratogenicity. Phenytoin, phenobarbital, primidone, ethosuximide, and carbamazepine have been implicated in oral contraceptive failure. These anticonvulsants induce the hepatic cytochrome P450 microsomal enzyme system, which, in turn, accelerates catabolism of endogenous and exogenous sex hormones. In addition, the anticonvulsants augment the synthesis of sex hormone-binding globulins, resulting in reduced levels of circulating free (active) hormone. Anticonvulsants may also promote the clearance of sex hormones by influencing sulfate conjugation and glucuronidation of the latter in the gut wall and liver. Oral contraceptive failure does not occur with valproic acid, which may actually inhibit cytochrome P450 enzymes, causing elevations in plasma steroid concentrations. Valproic acid, however, may cause hyperandrogenism and polycystic ovaries. Of the newer antiepileptic medications, lamotrigine, gabapentin, vigabatrin, levetiracetam, zonisamide, clobazam, and lacosamide do not induce the hepatic P450 microsomal enzyme system, and oral contraceptive failure is less likely to occur with concomitant use of these drugs. Topiramate and felbamate have modest effects on sex hormone pharmacokinetics and may affect contraceptive efficacy. Although breakthrough bleeding has been reported with tiagabine, the impact of this drug on ovarian hormone metabolism is believed to be minimal.

The course of epilepsy and its management may be greatly influenced by specific phases of the reproductive cycle and exposure to steroid contraceptives. A variety of seizure disorders have been documented to worsen around the time of ovulation or premenstrually (catamenial epilepsy) and during pregnancy. An increased risk of epilepsy is associated with menstrual irregularity around age 20. Curiously, left-sided temporal lobe seizures appear more likely to cluster at the onset of menses than right-sided temporal seizures, which tend to occur more randomly throughout the cycle. Data amassed from human and animal studies indicate that estrogens and progestins have epileptogenic and anticonvulsant properties, respectively. Estrogen augments glutamatergic and suppresses GABAergic neurotransmission, favoring epileptogenesis, whereas progesterone has the opposite effects. A rising estrogen—progesterone ratio during the late luteal phase may trigger catamenial seizure activity. Furthermore, the markedly elevated estrogen—progesterone ratio characteristic of the polycystic ovary syndrome may, in part, contribute to the relatively frequent association of this reproductive disorder with temporal lobe epilepsy. Exposure to oral contraceptives consisting of estrogen—progestin combinations does not appear to worsen seizure control significantly. However, spikes in circulating estrogen concentrations accruing from gonadotropin therapy for assisted reproduction may exacerbate seizures in women with epilepsy. Also of concern are interactions between enzyme-inducing anticonvulsants and hormones used for gender-affirming treatment in transgender persons. Management strategies for catamenial epilepsy include (1) premenstrual or periovulatory supplementation of anticonvulsant doses or addition of an adjunctive antiepileptic drug such as clobazam; (2) cyclic administration of acetazolamide, a mild diuretic with weak antiepileptic activity; and (3) progesterone supplementation by mouth or suppository. The allopregnanolone analogue ganaxolone (3α-hydroxy-3β-methyl-5β-pregnane- 20-one), a positive allosteric modulator of GABA-A receptors, may diminish epileptic activity in adults with partial-onset seizures and children with refractory infantile spasms. This neurosteroid appears to be well tolerated and, importantly, lacks hormonal activity.

With respect to gestational epilepsy, factors such as maternal sleep deprivation, stress, and inadequate anticonvulsant levels are probably more important than direct hormonal epileptogenesis. During pregnancy, serum levels of phenytoin, phenobarbital, and valproic acid may decrease by 30 to 40 percent of pregestational levels, with a lesser decline in carbamazepine. Primidone levels are reportedly stable during pregnancy, but the concentration of primidone-derived phenobarbital is reduced. Decreased drug compliance, bioavailability, and protein binding, as well as an increased volume of distribution and metabolic clearance, are factors contributing to the fall in anticonvulsant levels during pregnancy. The influences of the menstrual cycle and of oral contraceptive preparations on anticonvulsant disposition appear to be of minor clinical significance.

Movement Disorders

CHOREA

Pregnancy and steroid contraceptive therapy have infrequently been complicated by the acute or subacute development of choreiform movements of the face and extremities associated with limb hypotonia and pendular reflexes. Fever, dysarthria, and neuropsychiatric symptoms may complete the clinical picture. Gestational and oral contraceptive-related chorea have a close association with previous rheumatic fever and Sydenham chorea.

Estrogen-containing medications may elicit chorea in patients with a history of congenital cyanotic heart disease, Henoch–Schönlein purpura, systemic lupus erythematosus, and antiphospholipid antibody syndrome and exacerbate dyskinesias in chorea-acanthocytosis. Pharmacologic, epidemiologic, and pathologic evidence suggests that altered hormonal patterns characteristic of pregnancy and ingestion of oral contraceptives may unmask latent chorea by modulating dopaminergic neurotransmission in basal ganglia previously damaged by rheumatic or hypoxic encephalopathy. In most cases, chorea gravidarum and oral contraceptive-related dyskinesias resolve completely by the end of pregnancy or after discontinuation of the medication, respectively. As many as 20 percent of women experience recurrences of chorea with subsequent pregnancies. Patients with chorea gravidarum are at increased risk of later developing oral contraceptive-related dyskinesias, and vice versa.

In patients with suspected chorea gravidarum, appropriate clinical and laboratory investigations may be required to exclude other causes of chorea, such as acute rheumatic fever, systemic lupus erythematosus, hyperthyroidism, and Wilson disease. Chorea gravidarum is usually self-limited, and abortion or premature delivery is rarely indicated. Judicious use of neuroleptics or other medications may afford symptomatic relief in severe cases. Women with a history of gestational or oral contraceptive-induced chorea should probably minimize further exposure to any estrogen-containing medications.

PARKINSONISM

There are anecdotal reports in the early clinical literature of motor deterioration in idiopathic and neuroleptic-induced parkinsonism after exposure to exogenous estrogen. Furthermore, premenopausal women were reportedly more susceptible to drug-induced parkinsonism than men of similar age. These observations argued for a potentially antidopaminergic role of estrogen in this condition. Yet, in subsequent studies of premenopausal women with idiopathic Parkinson disease, motor symptoms were noted to worsen premenstrually when estrogen titers were falling, favoring a stimulatory influence of estrogen on striatal dopamine. Data from several studies suggest that postmenopausal estrogen replacement is beneficial in women with Parkinson disease. In other studies, postmenopausal estrogen therapy either had no significant dopaminergic effect or was associated with worsening motor scores. Epidemiologic studies suggested that early menopause (natural or surgical) may be a risk factor for the development of Parkinson disease and that the latter may be offset by postmenopausal estrogen replacement. However, larger prospective studies have disclosed no evidence of a beneficial effect of exogenous or endogenous estrogens on the risk of developing Parkinson disease. Exposure to oral contraceptives may be a risk factor for the disease, and polymorphisms of the estrogen receptor-β gene (an important mediator of estrogenic effects on the nigrostriatal pathway), although not associated with an overall risk of contracting Parkinson disease, may impact the age of symptom onset. Several studies have documented that exposure to the antiestrogen tamoxifen may substantially augment the risk of contracting Parkinson disease in women with breast cancer. Of potential therapeutic relevance, CSF and plasma concentrations of allopregnanolone are reportedly low in idiopathic Parkinson disease and this neurosteroid stimulates neurogenesis in the substantia nigra, modulates dopamine release, and improves motor control in animal models of the disease.[2]

WILSON DISEASE

Wilson disease is an inborn error of copper metabolism that is characterized by hepatic cirrhosis and degenerative changes in the basal ganglia. Patients exhibit decreased serum ceruloplasmin levels, increased plasma levels of nonceruloplasmin copper, and reduced biliary excretion of the heavy metal. Movement disorders, seizures, and psychosis result from the toxic effects of excessive copper deposition in neural tissues. In normal individuals, serum ceruloplasmin and copper levels increase during pregnancy and after administration of estrogen or estrogen–progestogen contraceptives. The rise in ceruloplasmin resulting from exposure to oral contraceptives is responsible for the green-tinged serum occasionally noted in these women. In patients with Wilson disease, increased serum ceruloplasmin levels occur during pregnancy and after treatment with exogenous estrogens. Effects on serum copper, however, are inconsistent. Normalization of serum ceruloplasmin levels by estrogen administration has no therapeutic benefit, and such exposure sometimes leads to neurologic deterioration. Exposure to hormonal contraceptives may yield "falsely normal" ceruloplasmin levels in patients with Wilson disease, resulting in a delay in diagnosis. Whether sex hormones similarly raise blood ceruloplasmin concentrations in other conditions featuring low levels of the protein, such as hypoceruloplasminemia and acquired copper deficiency, remains to be determined.

OTHER MOVEMENT DISORDERS

A broad spectrum of movement disturbances may be influenced by prior or current sex steroid exposure. Included are cases of posthypoxic and hereditary myoclonus, dominantly inherited myoclonic dystonia, tardive dyskinesia, hemiballismus, drop attacks, familial episodic ataxia, Gilles de la Tourette syndrome, the neuroleptic malignant syndrome, essential tremor, restless legs syndrome, and progressive supranuclear palsy.[3]

Nervous System Neoplasms

MENINGIOMAS

Meningiomas occur more frequently in women than men and are rarely diagnosed before puberty or during the senium, corresponding to the time of maximal gonadal activity. They are more common in patients with hormone-dependent breast carcinoma and in obese women, perhaps because of higher circulating estrogen levels derived from the aromatization of androstenedione to estrone in adipocytes. Meningiomas have been documented clinically and radiologically to undergo relatively rapid expansion during pregnancy, followed by spontaneous regression postpartum. Some women suffer exacerbations of symptoms in the luteal phase of the menstrual cycle. These fluctuations in tumor size have been attributed to steroid-induced fluid retention by the lesion, increased vascular engorgement of the tumor, and direct trophic effects of gonadal hormones on meningioma cells. Although there is an increase in the incidence of meningioma in women receiving HRT, this should not influence the practice of HRT as the overall frequency of meningiomas in this population remains low.

Numerous investigators have demonstrated the presence of progestin- and, to a lesser extent, estrogen- and androgen-binding proteins in a significant number of human meningioma specimens. These observations suggest that progestins and possibly other gonadal steroids may directly modify the growth and differentiation of these tumors. The presence of progestin receptors may indicate a more favorable prognosis because progesterone receptor-negative meningiomas have been associated with a greater tendency for brain invasiveness, higher mitotic indices and necrosis, and shorter disease-free intervals. Although the antiestrogen tamoxifen does not appreciably affect tumor size or neurologic status in patients with inoperable meningiomas, the antiprogestin RU486 has been reported to induce stabilization or regression of meningiomas, suggesting that antiprogesterone therapy may be useful in the management of these tumors. However, the effects of progestins and RU486 on meningioma growth in vitro are contradictory, and patients chronically treated with RU486 may require glucocorticoid replacement to counteract its antiglucocorticoid effects. Of note, gender-affirming treatment with estrogens, progestogens, or cyproterone acetate (a progestin with antiandrogen activity) may promote meningioma growth in transgender women.

GLIOMAS

There are anecdotal reports of astrocytomas enlarging during pregnancy, only to shrink spontaneously in the puerperium. As in the case of meningiomas, certain human gliomas may selectively bind estrogens, progestins, and androgens. Some may also contain enzymes (e.g., 17β-oxidoreductase and aromatase) that catalyze steroid hormone interconversions. The origin of putative steroid receptors in glial cell tumors is obscure, although significant numbers of normal astrocytes in certain brain regions possess estrogen receptors. Astroglial tumors predominantly express estrogen receptor-β, and expression levels reportedly decline with increasing histologic grade of malignancy. High-dose tamoxifen therapy may result in clinical and radiologic stabilization of astrocytomas and glioblastoma multiforme in some patients. These benefits are more likely to be due to the inhibitory effects of tamoxifen on protein kinase C or its role as a radiosensitizer than to any accruing antiestrogenic activity. Human oligodendrogliomas have also been reported to contain sex steroid receptors and could theoretically be subject to hormonal manipulations.

OTHER TUMORS

Acoustic neuromas, pituitary adenomas, and breast cancer metastases to the nervous system may also be responsive to sex hormones. Sex steroid receptors have also been reported in hemangioblastomas, anaplastic ependymomas, malignant lymphomas, melanomas, renal cell carcinomas, medulloblastomas, and primitive neuroectodermal tumors, suggesting that the natural history of these neoplasms may be influenced by sex hormones and their antagonists.

Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated demyelinating disorder of the central nervous system (CNS) that often occurs during the reproductive years. An association between specific *ESR1* gene polymorphisms and MS has been reported in some studies but not others and may be population dependent.

Epidemiologic studies have indicated that the overall effect of age at menarche, pregnancies, and breastfeeding on MS-related morbidity is nil.[4] As discussed in Chapter 31, subsequent studies involving larger patient cohorts have amply demonstrated a tendency for MS exacerbation during the first 3 postpartum months that is counterbalanced by significant suppression of disease activity in the third trimester. Indeed, the approximately 70 percent reduction in the relapse rate of MS in the third trimester is more robust than that accruing from interferon-β, glatiramer acetate, or intravenous immunoglobulin therapy. Immunomodulation that is necessary to prevent rejection of the semiallogenic fetus is probably responsible for the dampening of third-trimester disease activity in MS and other immune-mediated conditions. Factors that have been implicated in gestational immunosuppression include estradiol, progesterone, human chorionic gonadotropin, human placental lactogen, cortisol, 1,25-dihydroxyvitamin D_3, α-fetoprotein, pregnancy-associated glycoprotein, "blocking antibodies," immune complexes, and interleukin-10. If necessary, intravenous steroids can be used for MS attacks in pregnancy. Interferon-β should be discontinued 3 months before planned conception and should not be used during pregnancy or while breastfeeding.

Earlier age at puberty may be a predisposing factor for MS in girls but not boys. Although the risk of developing MS does not appear to be impacted by oral contraceptive use, the latter may delay the onset of the disease. The disease-modifying therapies dimethyl fumarate and fingolimod do not appear to diminish the effectiveness of hormonal contraception. Less is known regarding the potential impact of cladribine and anti-MS biologics on sex steroid metabolism. Finally, there are early studies reporting potentially beneficial effects of oral estriol in women with MS.

Alzheimer Disease

Alzheimer disease is a common dementing illness characterized by progressive neuronal degeneration, gliosis, marked depletion of acetylcholine and other neurotransmitter disturbances, and the accumulation of senile (amyloid) plaques and neurofibrillary tangles in discrete regions of the basal forebrain, hippocampus, and association cortex. By the turn of the millennium, there were promising reports suggesting that estrogens play an important role in normal human cognition, have a salutary effect on the manifestations of Alzheimer disease, and may even protect against the development of this neurodegenerative disorder in women. Fundamental research indicates that estrogens exert trophic influences on cholinergic neurons of the rodent basal forebrain, induce dendritic spines (synapses) and functional *N*-methyl-D-aspartate (NMDA) receptors (important for memory) in adult rat hippocampus, and induce massive neuritic growth in rodent hypothalamic explants. In addition, estrogens were shown to manifest antioxidant properties, reduce the deposition of fibrillar β-amyloid, modulate apolipoprotein E expression, suppress inflammatory responses implicated in neuritic plaque formation, increase cerebral blood flow and glucose utilization (which are deficient in subjects with Alzheimer disease) and stabilize microRNA expression patterns and mitochondrial bioenergetics.[5] There is also accumulating evidence that estrogens improve cognitive behaviors in rats and monkeys; that psychometric performance in women is influenced by the menstrual cycle phase; that transgender hormone therapy affects cognition in transsexual men and women; and that estrogen replacement therapy augments verbal memory scores in normal menopausal women. Moreover, early clinical studies suggested that estrogen replacement therapy may improve cognitive performance, especially language function, verbal memory, and attention, in menopausal women with Alzheimer disease, and enhance the likelihood of a beneficial response to acetylcholinesterase inhibitors in affected women. In several studies, postmenopausal estrogen replacement therapy appears to be associated with a significantly decreased risk of developing Alzheimer disease. There was some indication that postmenopausal estrogen replacement therapy protected against the development of dementia in women with Parkinson disease and that androgen (testosterone) or estrogen treatment conferred cognitive benefits in elderly men with Alzheimer disease or mild cognitive impairment. Lower postmenopausal estradiol levels have also been associated with increased risk of dementia in persons with Down syndrome.

The results of other large, randomized, placebo-controlled prospective trials evaluating the potential benefits of sex HRT in preventing the dementia of Alzheimer disease have been disappointing. Age-adjusted cognitive function scores are no different in women with coronary artery disease who received estrogen and progestin than in placebo-treated controls. Some studies have even demonstrated a slightly higher risk of dementia with HRT compared with placebo-treated controls. Of note, certain polymorphisms of the follicle-stimulating hormone receptor may confer protection against the disease in women (but not men).

The third Canadian Consensus Conference for the Diagnosis and Treatment of Dementia (2006) recommended against the use of estrogen/progestin replacement therapy for reducing the risk of dementia in postmenopausal women. It was also concluded that there is insufficient evidence for or against prescription of androgen replacement for cognitive dysfunction in elderly men. Since these recommendations were published, it has been hypothesized that there may be a critical perimenopausal "window" during which HRT may protect against the development of Alzheimer disease.[5] Importantly, the purportedly salutary influences of estrogen on cognition and hippocampal volumes may be offset in aging women bearing one or two copies of the apolipoprotein E ε4 allele. Regarding androgens, higher serum levels of bioavailable testosterone in late life predict a diminished risk of developing Alzheimer disease in men, perhaps due to androgen-induced down-modulation of brain β-amyloid deposition. Prospective clinical trials amply powered to determine the efficacy of androgen treatment in forestalling dementia in men (and possibly women) may be warranted.

Neurosteroidogenesis has also been implicated in the pathophysiology of Alzheimer disease. There are reports of reduced levels of DHEA-S in the plasma and cerebrospinal fluid and allopregnanolone concentrations in the prefrontal cortex of persons with Alzheimer disease. Allopregnanolone may contribute to cognitive well-being insofar as it suppresses neuroinflammation (microglial activation), diminishes β-amyloid pathology, increases hippocampal neurogenesis, and reverses learning and memory deficits in animal models of Alzheimer disease.

Neuropsychiatric Disorders

THE PORPHYRIAS

The porphyrias are characterized by the excessive production of porphyrins and porphyrin precursors resulting from specific enzymatic defects in the heme biosynthetic pathway. Neurologic manifestations, when present, include seizures, neuropsychiatric symptoms, and sensorimotor and autonomic neuropathies. Estradiol and other steroids with a 5β configuration induce the enzyme δ-aminolevulinic acid synthase and may thereby precipitate porphyric crises. Oral contraceptives increase urinary excretion of this enzyme in normal individuals, and it has been suggested that asymptomatic relatives of patients with porphyria should avoid oral contraceptives. In many women with acute intermittent porphyria, cyclic attacks of variable severity occur during the late luteal phase or, less commonly, at ovulation. New-onset acute intermittent porphyria has also been reported as a result of controlled ovarian hyperstimulation for in vitro fertilization. Paradoxically, some patients exhibit prolonged remissions after suppression of ovarian cyclicity with oral contraceptives.

Although acute treatment with gonadotropin-releasing hormone (GnRH) agonists, such as d-His or leuprolide, stimulates the pituitary–ovarian axis, chronic administration of these agents downregulates gonadotrope GnRH receptors, resulting in long-term suppression of pituitary–ovarian function. d-His administration (5 μg subcutaneously daily) yielded complete remission of severe premenstrual acute intermittent porphyria for the duration (8 months) of therapy in a single patient; similar benefits were observed in subsequent cases of catamenial acute intermittent porphyria and hereditary coproporphyria in response to GnRH analogue therapy. Side effects of long-term GnRH treatment include hot flashes, diminished breast size, and bone demineralization. GnRH analogues, unlike sex steroids, do not appear to induce porphyrin accumulation in chick embryo hepatic cell culture and provide a rational approach to the management of catamenial porphyria.

PREMENSTRUAL SYNDROME

The premenstrual syndrome (or premenstrual dysphoric disorder) occurs in approximately 30 percent of women during their reproductive years. Common neuropsychiatric symptoms include headache, fatigue, depression, irritability, increased thirst or appetite, and craving for sweet or salty foods. Symptoms typically begin toward the end of the luteal phase of the cycle and usually, but not invariably, resolve with the onset of flow. The pathophysiology of this disorder remains obscure. An increased luteal-phase estrogen–progesterone ratio, hyperprolactinemia, disturbances of the renin–angiotensin–aldosterone axis, hypothyroidism, and abnormal secretion of opioid peptides are among the causes considered for this enigmatic condition.

Numerous hormonal and nonhormonal therapies—including natural progesterone, oral contraceptives, bromocriptine, GnRH agonists, diuretics, drospirenone, prostaglandin inhibitors, vitamin B_6, calcium supplements, *Vitex agnus castus* (chasteberry), selective serotonin reuptake inhibitors, and lithium—are prescribed for the management of premenstrual syndrome. In many cases, the efficacy of these treatments remains uncertain. Induction of "artificial menopause" with a GnRH agonist (d-Trp-Pro-NEt-Gn-RH, 50 μg/day subcutaneously) relieves both physical and neuropsychiatric symptoms in women with rigorously defined premenstrual syndrome; prolonged hypoestrogenemia resulting from the long-term use of these agents may predispose to osteoporosis. Such therapy should probably be reserved for patients with incapacitating symptoms, and low-dose estrogen replacement may have to be considered when the duration of treatment exceeds several months. Continuous daily administration of levonorgestrel 90 μg/ethinyl estradiol 20 μg is well tolerated and possibly useful in controlling the physical, psychologic, and behavioral symptoms of the premenstrual syndrome.

DEPRESSION AND PSYCHOSIS

Depression and other major affective disorders may surface in relation to the menstrual cycle, the puerperium, and menopause. Approximately 15 percent of women experience postpartum depression, whereas 50 to 80 percent report milder dysphoria ("maternal blues"). In patients with postmenopausal depression, mood elevation and anxiolysis often occur promptly in response to estrogen replacement. Paradoxically, oral contraceptives may precipitate depression in susceptible individuals. Estrogen has also been implicated in the pathogenesis of anorexia nervosa because of the high preponderance of this condition in women and the potent anorexic effects of estrogen in animals.

Psychotic disorders characterized by extreme agitation, hallucinations, paranoid delusions, incoherent speech, and mood lability may arise during the postpartum period, may recur consistently during the late luteal phase of the cycle, and may complicate withdrawal of estrogen replacement therapy in transgendered women. Such disorders may be refractory to conventional therapies (e.g., neuroleptics, lithium, electroconvulsive treatment) but may respond well to specific hormonal interventions, including the use of oral contraceptives, intramuscular progesterone, and danazol. "Menopause" induced by GnRH analogues may also be of considerable benefit in the management of cyclical psychosis. Transdermal estradiol has been shown to be an effective adjunctive therapy for women of childbearing age with treatment-resistant schizophrenia. Furthermore, adjuvant therapy with tamoxifen reduces the frequency of manic episodes in patients with bipolar disease, and the estrogen receptor modulator raloxifene ameliorates cognitive and psychologic deficits in men and women with schizophrenia. Estrogen receptor-α polymorphisms have been associated with symptoms of autism in Chinese Han children, although little is known concerning the clinical effects of sex hormone manipulation in persons with autistic spectrum disorders.

Sleep Disorders

Estrogen and progestin replacement may shorten mean sleep latencies, extend the duration of rapid-eye-movement sleep periods, and diminish nocturnal movement arousals, thereby improving sleep in hypogonadal women. The GABA-active metabolites allopregnanolone and pregnanolone may mediate the reduction in vigilance during wakefulness observed after the administration of progesterone to healthy men. Progestins may also provide stimulatory drive to brainstem respiratory centers in subjects with central sleep apnea and thereby improve hypoventilation. The hypocapnic apnea threshold is lower in women than men, and testosterone administration increases this threshold in premenopausal women. In men, obstructive sleep apnea may correlate with low serum testosterone levels. Menopause has been associated with attenuation of circadian rhythmicity and an increase in sleep-disordered breathing. Estrogen plus progesterone has been shown to decrease the prevalence of nocturnal arousals, breathing irregularities, periodic limb movements, hot flashes, and bruxism.

Intracranial Hypertension

Progesterone suppresses post-traumatic cerebral edema and intracranial hypertension in rodents. This progestational effect has been attributed to reduction in blood–brain barrier permeability and inhibition of cerebrospinal fluid production by the choroid plexus. Estrogens, by contrast, appear to enhance cerebral endothelial cell permeability and post-traumatic brain edema in female rats. Estrogenic attenuation of the blood–brain barrier may also play a role in the pathogenesis of pseudotumor cerebri (idiopathic intracranial hypertension) in humans and explain the robust female predilection for this disorder. Idiopathic intracranial hypertension may be over-represented in women with the polycystic ovarian syndrome and hyperandrogenism, and in female-to-male transgender persons receiving intramuscular testosterone. Data concerning the risk of pseudotumor cerebri in women exposed to hormonal contraception are conflicting.[6]

Neuromuscular Diseases

Catamenial Sciatica

Ectopic endometrial tissue (endometriosis) is hormone sensitive and undergoes epithelial sloughing and hemorrhaging at the time of menses. Ectopic endometrial tissue may destroy lumbar vertebrae, producing back pain, invade the lumbosacral plexus in the retroperitoneal space, and implant within the sheath of the sciatic nerve. In this last instance, radicular pain in the distribution of the nerve usually begins 2 to 3 days before the onset of menses and may continue for a variable duration after cessation of flow (catamenial sciatica). In addition to pain, there is often numbness, weakness, and loss of ankle reflexes. In contrast to far more common discogenic radiculopathy, endometriotic sciatica is less likely to respond to bed rest, and the imaging findings are usually unimpressive. There may be evidence of endometriosis elsewhere, and surgical exploration of the sciatic nerve may be required for diagnosis. In positive cases, the nerve appears blue, and a dark hemorrhagic fluid is expressed after incision of the sheath. Biopsy specimens reveal characteristic glandular elements. Symptoms of catamenial sciatica may show dramatic improvement with standard therapy for endometriosis, including danazol, progestins, GnRH agonist, and in refractory cases, bilateral oophorectomy.

Other Neuromuscular Disorders

Endogenous and administered sex hormones (mainly estrogens) may influence the natural history of Bell palsy, recurrent brachial plexopathy, and carpal tunnel syndrome. Abnormally high estrogen levels have been reported in male patients with amyotrophic lateral sclerosis, Kugelberg–Welander disease, bulbospinal muscular atrophy (Kennedy syndrome), Duchenne muscular dystrophy, and the Crow–Fukase syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes [POEMS syndrome], usually associated with plasma cell dyscrasias). It is unclear whether hyperestrogenemia plays any significant role in the pathogenesis of these neuromuscular disorders. Initial results suggesting that the GnRH agonist leuprorelin improves swallowing in patients with bulbospinal muscular atrophy could not be confirmed in subsequent phase 3 studies. Dysfunction of testicular peritubular myoid cells and corpus cavernosum smooth muscle contributes to the hypergonadotropic hypogonadism and impotence that complicate myotonic dystrophy in men.

PITUITARY GLAND

The endocrine and nervous systems interact in intricate ways, and disorders in one system may cause dysfunction of the other in diverse ways. For example, small anterior pituitary tumors produce symptoms principally as the result of hormonal excess, but large tumors cause symptoms of either hypersecretion or hyposecretion as well as dysfunction of adjacent cranial nerves or cerebral structures. The protean clinical features of hormonal excess and deficiency states include both central and peripheral nervous system dysfunction.

The complex anatomy of the sellar region influences the clinical features of pituitary disorders.[7,8] The pituitary gland, or hypophysis, sits in a bony depression in the posterior sphenoid bone called the sella turcica, bounded anteriorly by the tuberculum sellae and anterior clinoid process and posteriorly by the dorsum sellae. Dural reflections border the pituitary superiorly and laterally. The diaphragma sellae forms the roof of the sella turcica and lies beneath the optic chiasm. Adjacent bilaterally is the cavernous sinus, through which passes the internal carotid artery and cranial nerves III, IV, V (upper two divisions), and VI. In addition the cavernous sinus serves to drain the ophthalmic and middle and inferior cerebral veins.

The anterior pituitary, or adenohypophysis, derives embryologically from Rathke pouch, of ectodermal origin, and has blood supplied by the hypophyseal-portal system. Hormones secreted by the anterior pituitary include prolactin, growth hormone (GH), adrenocorticotropic hormone (ACTH), thyrotropin (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The hypothalamus controls anterior pituitary hormone secretions through various hypophysiotropic substances, most of which are peptides (Table 20-1).[8] The hypophyseal-portal system provides the basis for feedback loops that regulate the hypothalamic–pituitary axis.

The posterior pituitary, known also as the neurohypophysis or pars nervosa, derives from a neuroectodermal extension of diencephalon that fuses with Rathke pouch. Also of neuroectodermal origin is the infundibulum linking the pituitary to the hypothalamus at the median eminence, which also forms the floor of the third ventricle. The inferior hypophyseal artery, a branch of the intracavernous carotid, supplies the neurohypophysis. Neurohypophyseal hormones include oxytocin and antidiuretic hormone (ADH) or arginine vasopressin.

The juxtaposition of the pituitary gland to hypothalamus, third ventricle, intracavernous carotid arteries, and cranial nerves related to vision, extraocular movements, and mid- and upper facial sensation accounts for many of the neurologic manifestations of lesions in and around the sella. Endocrine disturbances arising from excess or insufficient secretion of one or more pituitary hormones may also cause neurologic as well as systemic symptoms and signs, and laboratory abnormalities. Advances in neuroimaging have greatly facilitated assessment of sellar and parasellar lesions.[7] A detailed discussion of the increasingly complex array of stimulation and inhibition studies used to assess the integrity of specific elements of the hypothalamic–pituitary axis is provided elsewhere.[8] However, a basic understanding of pituitary hormone physiology is essential to evaluating patients with mass lesions in and around the gland and it is reviewed here after a discussion of the neurologic symptoms and signs resulting from these lesions.

TABLE 20-1 ■ Anterior Pituitary and Hypothalamic Hormones

Pituitary Hormone	Hypothalamic Factor
Prolactin	Dopamine (inhibitory)
Growth hormone (GH)	Growth hormone-releasing hormone (GHRH) Somatostatin (inhibitory)
Adrenocorticotropin (ACTH)	Corticotropin-releasing hormone (CRH)
Thyrotropin (TSH)	Thyrotropin-releasing hormone (TRH)
Luteinizing hormone (LH) and follicle-stimulating hormone (FSH)	Gonadotropin-releasing hormone (GnRH)

Sellar and Parasellar Lesions

Pituitary adenomas are the most common mass in the sellar region and account for up to 25 percent of intracranial neoplasms. Previous classification schemes based on histologic staining properties have given way to categorization based on hormone secretion.[8,9] Pituitary adenomas are also classified by size. Microadenomas (Fig. 20-2A), lesions that are 10 mm or smaller, typically spare adjacent neural or vascular structures and generally come to medical attention during evaluation for symptoms and signs of hormone oversecretion. Lesions larger than 10 mm, known as macroadenomas, or ≥40 mm, known as giant adenomas (Fig. 20-2B), also may present with manifestations of hormone excess (~two-thirds of pituitary adenomas) or may impair normal glandular function, resulting in hypopituitarism. When macroadenomas compress adjacent neural or

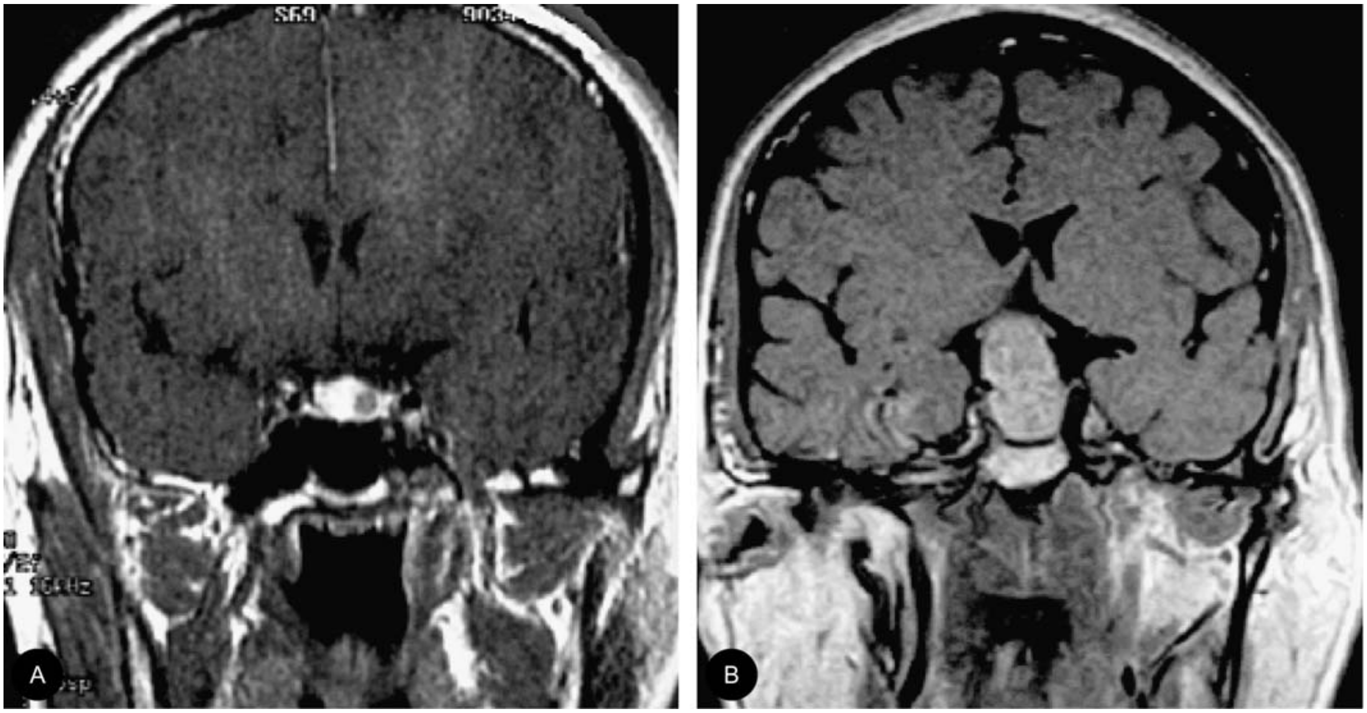

FIGURE 20-2 ■ Neuroimaging of pituitary adenoma. *A*, Microadenoma. Gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) shows a small focus of decreased enhancement compatible with microadenoma in a young woman with galactorrhea-amenorrhea. *B*, Macroadenoma. Large sellar lesion, subsequently shown to be a nonsecretory adenoma, in a gadolinium-enhanced T1-weighted MRI obtained in a middle-aged man with progressive visual loss.

vascular structures, neurologic dysfunction, such as headache, visual loss, ophthalmoparesis, and facial sensory symptoms, may develop.[7–9] Adenoma size does not correlate with headache, which may have features similar to migraine or trigeminal autonomic cephalgia. Macroadenomas extending superiorly may compress the optic chiasm, nerves, or tracts. Bitemporal hemianopia is the classic consequence, although monocular visual loss or junctional scotoma also may occur. Because adenomas grow slowly, patients may not appreciate visual deficits until they are quite advanced. Third ventricular extension occasionally causes acute or chronic hydrocephalus. Lateral extension, with subsequent cavernous sinus involvement, disturbs extraocular motility and sensation in the upper and middle face. Very large lesions involving inferior frontal or medial temporal lobes are rare but may cause cognitive impairment, behavioral changes, or seizures. A few pituitary tumors extend inferiorly, causing epistaxis or CSF rhinorrhea.

Pituitary adenomas account for 90 percent of masses in the sellar region, with other pituitary tumors, nonpituitary neoplasms, metastases, infectious and inflammatory disorders, vascular lesions, and cysts accounting for the rest (Table 20-2).[7] Craniopharyngiomas arise from epithelial cell rests of Rathke pouch. Among malignant lesions, pituitary carcinomas are quite rare, and metastases to the pituitary are recognized more frequently at autopsy than during life.

Among more common disorders, primary empty sella is often associated with an incompetent diaphragma sellae, which allows arachnoid and CSF to herniate into the sella. Typically an incidental finding on neuroimaging studies, primary empty sella syndrome is not usually associated with endocrinopathy. Secondary empty sella occurs after spontaneous or treatment-induced regression of pituitary disease. Other important non-neoplastic sellar lesions include granulomatous processes, such as tuberculosis or sarcoidosis, and vascular lesions such as aneurysms of the intracavernous carotid artery.

Magnetic resonance imaging (MRI) before and after gadolinium enhancement, with high-resolution thin sections in the sagittal and coronal planes, is the test of choice for pituitary-region imaging. On T1-weighted images, high signal intensity in the posterior pituitary is referred to as the “bright spot” and is

TABLE 20-2 ■ Differential Diagnosis of Sellar Masses

Neoplasms

- Pituitary origin
  - Anterior: pituitary adenoma or carcinoma
  - Posterior: granular cell tumor, stalk or posterior lobe astrocytoma
- Nonpituitary origin
  - Craniopharyngioma
  - Germ cell tumor
  - Meningioma
  - Glioma (hypothalamic, optic nerve, or chiasm)
  - Skull base: chordoma, giant cell tumor, fibrous dysplasia
- Others
  - Lipoma
  - Hemangioblastoma
  - Sarcoma
  - Schwannoma
  - Paraganglioma
  - Esthesioneuroblastoma
- Metastatic
  - Carcinoma
  - Melanoma
  - Hematopoietic malignancies

Vascular lesions

- Intracavernous carotid aneurysm
- Cavernous sinus thrombosis
- Pituitary apoplexy

Cysts

- Rathke cleft cyst
- Arachnoid cyst
- Epidermoid
- Dermoid

Inflammatory disorders

- Granulomatous: sarcoidosis, tuberculosis, syphilitic gumma, giant cell granuloma
- Pituitary abscess
- Lymphocytic hypophysitis
- Histiocytosis
- Mucocele

Empty sella syndrome

Pituitary hypertrophy

- Puberty (in girls)
- Pregnancy
- Chronic primary hypothyroidism

believed to represent ADH in neurosecretory vessels.[7] Pituitary adenomas typically enhance less intensely than normal glandular tissue (Fig. 20-2A). In patients who cannot undergo MRI, precontrast and postcontrast computed tomography (CT) images through the area can be obtained. A consequence of modern neuroimaging is detection of the asymptomatic pituitary mass, the so-called pituitary "incidentaloma."[9]

Anterior Pituitary

PROLACTIN

Prolactin acts on mammary tissue to promote lactation and inhibit cyclic gonadotropin secretion. Hypothalamic control of prolactin secretion occurs primarily by inhibition, and thus pituitary stalk disruption from lesions other than prolactinomas may elevate serum prolactin levels, although rarely above 200 μg/L (normal <25 μg/L).[8] Dopamine is the major inhibitory factor. Accordingly, neuroleptics and other dopamine antagonists can cause mild hyperprolactinemia, although the risk may be lower for some atypical antipsychotics; dopaminergic drugs are therefore used therapeutically to lower prolactin levels.[8,9] Prolactin-releasing factors are less well understood, although thyrotropin-releasing factor (TRH) plays a role. Consequently, in primary hypothyroidism, when TRH is elevated, the resulting hyperprolactinemia and pituitary enlargement may cause diagnostic confusion with prolactinoma.[9] The differential diagnosis of hyperprolactinemia (Table 20-3) also includes pregnancy, lactation, and chest wall stimulation.[8,9] Serum prolactin may be modestly increased in the first hour after a generalized tonic-clonic or complex partial seizure. However, recent studies of prolactin levels in patients with psychogenic nonepileptic spells suggest that elevated levels have limited usefulness in the differentiation of epileptic from nonepileptic seizures.

Amenorrhea-galactorrhea in women and impotence and decreased libido in men should prompt consideration of hyperprolactinemia. In the absence of venipuncture stress, an elevated serum prolactin level establishes the diagnosis, and further evaluation should include medication history and laboratory screening for chronic kidney disease and hypothyroidism. Prolactinomas account for approximately 50 percent of hormonally active pituitary adenomas.[9] Prolactin levels exceeding 250 μg/L suggest prolactinoma, with levels above 500 μg/L diagnostic of macroprolactinoma. Values lower than this may be seen with any type of macroadenoma due to stalk compression or as a consequence of the "hook effect," whereby the radioimmunoassay used to determine serum prolactin

TABLE 20-3 ■ Differential Diagnosis of Hyperprolactinemia

Physiologic
Pregnancy, lactation
Metabolic
Primary hypothyroidism, chronic kidney disease, cirrhosis, adrenal insufficiency
Medications—Neuroleptics, tricyclic antidepressants, SSRIs, verapamil, metoclopramide
Estrogens
Neurogenic
Chest wall injury, herpes zoster, breast stimulation, spinal cord lesion
Pituitary disease—acromegaly, Cushing disease
Prolactinoma, other pituitary adenomas or tumors, stalk section, granulomatous infiltration
Hypothalamic/Stalk Disease
Neoplastic, vascular, inflammatory, post-irradiation, severe head trauma
Seizures, stress, macroprolactinemia, idiopathic

returns a falsely low value in severe hyperprolactinemia.[8,9] Performing the assay with diluted serum samples reveals the true, markedly elevated prolactin level and should be requested when prolactin levels are not markedly elevated in a patient with a macroadenoma.

Amenorrhea-galactorrhea and infertility bring women to early medical attention, and thus microprolactinomas predominate. Symptoms of hypogonadism in men—impotence, loss of libido, and infertility—may not as reliably trigger measurement of serum prolactin level. Consequently, macroprolactinomas are more common in men, classically presenting with headache or visual impairment. Medical therapy with dopamine agonists decreases prolactin levels, reverses hypogonadism, and shrinks approximately 75 percent of macroprolactinomas and an even higher percentage of microprolactinomas.[9] Cabergoline is better tolerated and more effective than bromocriptine, and is thus the preferred drug. Surgery is typically reserved for patients with acute visual impairment or who do not improve or tolerate therapy with dopaminergic agents. As is the case for medical therapy, surgical outcomes are better for patients with microadenomas than macroadenomas. Trans-sphenoidal approaches are favored, although large, invasive tumors may require bifrontal craniotomy. Regardless of whether the treatment plans include medication, surgery, or both, patients require monitoring with serial clinical assessment, prolactin levels, visual field testing, and neuroimaging.[9] Radiation therapy is used primarily when medical and surgical approaches have been unsuccessful. Newer radiotherapy techniques may be safer or more effective than conventional radiotherapy.[10]

GROWTH HORMONE

Secretion of GH, a 191-amino-acid polypeptide, is regulated by stimulatory (GH-releasing hormone) and inhibitory (somatostatin) hypothalamic factors. Secretory dynamics are complex; factors that influence pulsatile GH secretion include age, nutritional state, and sleep. GH stimulates skeletal growth and exerts a variety of metabolic effects, including glucose intolerance. The action of GH is mediated by its receptors in liver, bone, and fat, as well as by induction of insulin-like growth factor I (IGF-I).

Excessive circulating GH before epiphyseal fusion in children leads to gigantism. In adults, sustained GH excess causes acromegaly, which results from pituitary hypersecretion in nearly all cases. Coarsened facial features and enlargement of hands and feet may only be recognized in retrospect and are an infrequent presenting complaint. The diverse systemic manifestations include hyperhidrosis, reproductive dysfunction, skin tags, colonic polyps, arthropathy, hypertension, hyperlipidemia, diabetes, and sleep apnea.[9] Neurologic symptoms include proximal weakness and compression of neural structures by bony and soft tissue overgrowth causing, for example, carpal tunnel syndrome.[8–10] Macroadenomas are identified in most cases, and symptoms of an expanding sellar mass may bring patients to clinical attention. The pulsatile nature of GH secretion limits the diagnostic utility of random GH determination, hence elevated serum IGF-1 level establishes the biochemical diagnosis of acromegaly. Autonomous GH secretion may be demonstrated by lack of appropriate GH suppression during an oral glucose tolerance test. Other important diagnostic tests include neuroimaging studies, visual field testing, serum prolactin level, and evaluation for panhypopituitarism and complications of acromegaly, in particular cardiovascular and bony disease, and colonic polyps.

Cosmetic disfigurement and chronic pain impair quality of life, and patients with untreated acromegaly risk premature death from diabetes, hypertension, cardiovascular disease, and colon cancer. Normalizing GH and IGF-1 is the therapeutic goal, and decreases long-term mortality. Trans-sphenoidal resection is the primary treatment of choice for microadenomas and macroadenomas. Expert pituitary neurosurgeons can normalize GH and IGF levels with reduction or elimination of tumor mass in 80 to 90 percent of microadenomas and 40 to 60 percent of macroadenomas. Options for adjunctive medical therapy include the dopamine agonist cabergoline and somatostatin analogues octreotide, lanreotide, or pasireotide, alone or in combination. The GH receptor antagonist pegvisomant can normalize IGF-1 levels in many patients, but does not have any effects on tumor growth or size. Medical therapy is usually used after surgery to control GH and IGF-1 levels, or, in selected cases, to shrink large tumors before planned surgery or when surgery is not possible. Conventional radiotherapy, stereotactic radiosurgery, or repeat surgical resection may be necessary if GH levels remain elevated.

Adrenocorticotropic Hormone and Cushing Disease

ACTH is a 39-amino-acid peptide derived from pro-opiomelanocortin, a precursor molecule that also gives rise to β-endorphin and β-lipotropin. Corticotropin-releasing hormone (CRH), secreted by the hypothalamus, controls ACTH release. ACTH stimulates adrenal steroidogenesis in a circadian pattern. ACTH and cortisol levels are highest in the morning and lowest in late evening; psychologic or physiologic stress also activates the pituitary–adrenal axis.

Cushing disease is due to ACTH hypersecretion from a pituitary adenoma and is a common cause (65 to 70%) of endogenous hypercortisolism.[9,11] Clinical features include central obesity, dorsocervical fat pad ("buffalo hump"), hypertension, bruising, purple abdominal striae, thin skin, facial plethora, hyperpigmentation, acne, hirsutism, osteoporosis, menstrual disorders, impotence, decreased libido, and infections. Cushing disease is associated with an increase in mortality. Laboratory findings include hypokalemia, hyperglycemia, and peripheral leukocytosis. Neurologic manifestations include myopathy, headache, neuropsychiatric disturbances including particularly mood disorders and cognitive impairment, and less commonly spinal epidural lipomatosis with resulting radiculopathy or myelopathy.[9,11]

Diagnosis depends on demonstrating endogenous hypercortisolism and then localizing the source of excess ACTH secretion to the pituitary. Recommended screening tests include urinary free cortisol, late-night salivary cortisol, or either the 1-mg overnight or longer low-dose (2 mg/day for 48 hours) dexamethasone suppression test. The 24-hour urinary free cortisol measurement has lower sensitivity and specificity and may yield false-positive results. Pregnancy, depression, alcoholism, morbid obesity, glucocorticoid resistance, and poorly controlled diabetes mellitus can cause hypercortisolism without Cushing syndrome, as can stress (including hospitalization or intense exercise), and malnutrition. A second screening test is often needed. Dexamethasone testing can be confounded by agents that alter steroid clearance, including some antiepileptic drugs. Distinguishing pituitary from ectopic ACTH secretion can be difficult, and inferior petrosal sinus sampling aids diagnosis in centers experienced in its use. Brainstem infarctions or hemorrhages are rare but serious complications of this procedure. Most tumors in Cushing disease are microadenomas and, in up to half of patients, not apparent on MRI.

Trans-sphenoidal surgery is the treatment of choice, with remission rates of 65 to 95 percent for microadenomas and recurrence rates of 10 to 20 percent at 10 years.[9] Remission rates are lower for macroadenomas, which recur earlier and more frequently than smaller tumors. Transient or permanent adrenal insufficiency frequently develops postoperatively. Among options available for patients with persistent hypercortisolism after surgery are repeat surgery, conventional radiotherapy or stereotactic radiosurgery, and medical therapy. Ketoconazole, metyrapone, mitotane, and etomidate inhibit adrenal steroidogenesis. Agents which target the pituitary include the somatostatin analogues (e.g., pasireotide) and the dopamine agonist cabergoline. Bilateral total adrenalectomy can be performed laparoscopically and is another treatment option; however, it obligates permanent adrenal replacement therapy and carries the risk of Nelson syndrome, in which an ACTH-secreting pituitary adenoma enlarges rapidly due to loss of corticosteroid inhibition.

Thyroid-Stimulating Hormone

Pituitary adenomas secreting TSH cause hyperthyroidism and are rare, with an estimated incidence of one case per million. Clinical manifestations are those of hyperthyroidism (Chapter 18), with goiter in most cases, as well as features referable to an enlarging pituitary mass, as most are macroadenomas. Concomitant prolactin or GH hypersecretion occurs in some patients and hence galactorrhea-amenorrhea or features of acromegaly may co-exist. TSH is inappropriately normal or elevated for the high peripheral thyroid hormone levels, distinguishing these lesions from Graves disease or toxic goiter. Individuals with thyroid hormone resistance have elevated laboratory studies suggesting central hyperthyroidism, but generally lack clinical manifestations of hyperthyroidism. For TSH-secreting pituitary tumors, surgical resection is the preferred primary therapy. If thyroid hormones remain elevated postoperatively, radiotherapy, radiosurgery, or somatostatin analogues may be used as adjunctive therapy. Thyroidectomy or antithyroid drugs such as methimazole or propylthiouracil risk increasing tumor growth by interfering with feedback inhibition.

Clinically Nonfunctioning Pituitary Adenomas

Most pituitary tumors that are unaccompanied by clinical evidence of hormonal hypersecretion are gonadotroph cell adenomas, which inefficiently secrete gonadotropins or discordantly secrete their α, FSH-β, or LH-β subunits.[8,9] With the paucity of endocrine symptoms, most are macroadenomas or incidentalomas detected as incidental findings on neuroimaging obtained for other indications. Presenting features are those of a large pituitary mass: headache, visual dysfunction, and hypopituitarism due to compression of normal pituitary or the portal system. Serum prolactin, assessment of anterior pituitary function, and visual field testing should accompany neuroimaging studies. Surgery is the primary therapy of choice for patients with macroadenoma with symptomatic mass effects, with additional radiotherapy for significant residual tumor or recurrence.[10] Nonsecreting microadenomas rarely grow in size and can be monitored with serial MRI scans. If adenomas abut the optic nerves, visual fields should be monitored at regular intervals.

The clinical and therapeutic features of pituitary adenomas are summarized in Table 20-4.

Pituitary Apoplexy

Headache and visual loss, variably accompanied by oculomotor dysfunction, nausea, vomiting, altered mentation, and meningismus, constitute the classic clinical features of pituitary apoplexy, caused by pituitary hemorrhage or infarction. The presenting syndrome may be fulminant, resembling subarachnoid hemorrhage, but subacute or even asymptomatic forms have been recognized increasingly. Headache, visual loss (frequently decreased acuity or bitemporal hemianopia), and diplopia are common, and most patients have impairment of at least one anterior pituitary hormone. Acute adrenal insufficiency may be fatal, hence empiric corticosteroid replacement should be given to all patients with pituitary apoplexy. Hypogonadism and hypothyroidism are common, as is hyponatremia.

Pituitary apoplexy often occurs in adenomas, including those that have been clinically silent, and the risk of symptomatic apoplexy is higher in patients with macroadenomas. Although most cases develop without obvious cause, reported precipitating factors include anticoagulation, trauma, dynamic hormone testing of pituitary function, radiation, and dopamine agonist treatment or its cessation. Sheehan syndrome refers to ischemic pituitary necrosis after postpartum hemorrhage and hypotension.

The differential diagnosis of pituitary apoplexy includes subarachnoid hemorrhage, bacterial meningitis, cavernous sinus thrombosis, and upper brainstem infarction or hemorrhage. Sellar MRI is the neuroimaging study of choice, although CT may be diagnostic when MRI is unavailable or contraindicated. CSF shows nonspecific abnormalities. Transsphenoidal decompression should be undertaken in patients with significant visual field deficit, loss of visual acuity, or deteriorating mental status. Surgery may also help to preserve pituitary function. Once the acute illness has resolved, patients should be monitored for hypopituitarism, with hormone replacement instituted as needed.

Posterior Pituitary

Magnocellular neurons of the hypothalamic supraoptic and paraventricular nuclei synthesize precursor polypeptides, which ultimately are cleaved to form the posterior pituitary hormones oxytocin and ADH.[12] Oxytocin mediates the “let-down” reflex of milk

TABLE 20-4 ■ Diagnosis and Management of Pituitary Adenomas

Type of Adenoma	Presenting Symptoms	Predominant Tumor Type	Primary Therapy	Adjunctive Therapy	Comments
Prolactin-secreting	Children: delayed puberty Women: amenorrhea-galactorrhea, infertility Men: headache, visual loss, impotence	Women: microadenoma Men: macroadenoma	Dopamine agonists	Surgery, radiotherapy, radiosurgery	Most common pituitary adenoma
GH-secreting	Children: gigantism Adults: acromegaly	Macroadenoma	Surgery	Somatostatin analogues, GH receptor antagonist, dopamine agonists, radiotherapy, radiosurgery	Increased mortality, improves with treatment
ACTH-secreting	Central obesity, hypertension, purple striae, bruising, osteoporosis, cognitive and mood changes, myopathy	Microadenoma	Surgery	Steroidogenesis inhibitors, somatostatin analogues, dopamine agonists, radiotherapy, radiosurgery	Untreated disease associated with increased mortality
TSH-secreting	Hyperthyroidism, goiter	Macroadenoma	Surgery	Somatostatin analogues, radiotherapy, radiosurgery	Rare
Nonsecreting	Headache, visual loss, hypopituitarism Incidental finding on CT or MRI obtained for other indications (usually microadenoma)	Macroadenoma	Surgery (serial imaging for microadenomas)	Radiotherapy, radiosurgery	Most secrete gonadotroph subunits

ACTH, adrenocorticotropic hormone; GH, growth hormone; TSH, thyrotropin.

expulsion in response to suckling. ADH facilitates tubular water resorption, thus controlling renal free water clearance and, in concert with hypothalamic thirst mechanisms, regulates water balance and osmolality. Deficient or inappropriate ADH secretion may complicate cerebral disorders or their treatment and lead to neurologic disturbances.

Diabetes Insipidus

Diabetes insipidus is characterized by excessive renal water loss due to ADH (arginine-vasopressin) deficiency. Awake patients present with thirst, polydipsia, and polyuria. ADH hyposecretion leads to central diabetes insipidus, and deficient renal response to adequate circulating ADH levels causes nephrogenic diabetes insipidus. Both types of diabetes insipidus have congenital and acquired forms (Table 20-5) and must be distinguished from excessive water drinking, in which polyuria is appropriate to water intake. Awake patients with diabetes insipidus can often increase their fluid intake sufficiently to compensate for urinary losses. Patients who cannot maintain adequate water intake to balance polyuria develop hypernatremia, volume contraction, and encephalopathy. Brain shrinkage in severe

TABLE 20-5 ■ Causes of Diabetes Insipidus

Central Causes

- Acquired
  - Trauma and neurosurgery
  - Parasellar pathology
    - Neoplasms
    - Granulomatous disorders
    - Vascular lesions
    - Autoimmune: lymphocytic hypophysitis, autoimmune hypothalamic disease
  - Cerebral infection
  - Hypoxic-ischemic brain injury
  - Stroke
  - Pregnancy
  - Idiopathic
- Congenital/familial
  - Septo-optic dysplasia
  - Laurence–Moon–Biedl syndrome
  - Wolfram syndrome
  - ADH mutations

Nephrogenic causes

- Acquired
  - Metabolic
    - Hypercalcemia
    - Hypokalemia
  - Drugs
    - Lithium
    - Antibiotics: demeclocycline, amphotericin B, foscarnet
    - Others: colchicine, loop diuretics
  - Chronic renal parenchymal disease
    - Autoimmune
    - Amyloidosis
    - Sickle cell anemia
  - Postobstructive uropathy
- Congenital/familial
  - ADH receptor mutations
  - Aquaporin-2 mutations

ADH, antidiuretic hormone.

hypertonic encephalopathy may lead to intracerebral hemorrhage.

Common acquired causes of central diabetes insipidus include trauma, cerebral hypoxia-ischemia, and neoplastic, granulomatous, and inflammatory disorders of the sellar region. Transient diabetes insipidus is not uncommon after head trauma or neurosurgery. Most acquired nephrogenic causes are metabolic or toxic, including hypokalemia, hypercalcemia, and lithium. Diagnosis depends on demonstrating an inability to appropriately concentrate urine and is suggested by passage of large amounts of dilute urine. However, polyuria alone is not sufficient to make the diagnosis. In critically ill patients with increased intracranial pressure, for example, polyuria may reflect osmotic diuresis from mannitol therapy, rather than diabetes insipidus. Low urine osmolality in the presence of polyuria and hypertonicity in serum indicates inability to concentrate urine in severe diabetes insipidus, but the diagnosis can be challenging in milder disease. Water deprivation tests, monitoring urine and serum osmolality in the presence of dehydration, are sometimes necessary, but are not without risk, especially in children. The response, after water deprivation, to exogenously administered desmopressin (DDAVP), the ADH analogue, indicates whether the diabetes insipidus is central or nephrogenic. One diagnostic approach to distinguish pituitary diabetes insipidus from primary polydipsia, the AVP-MRI method, can be performed on an outpatient. If plasma ADH is low, when urine osmolarity is low, brain MRI can determine if the posterior pituitary bright spot is absent or small, indicating pituitary diabetes insipidus. If the bright spot is normal or enlarged, it may indicate primary polydipsia.

For both the central and nephrogenic disorders, correcting the water deficit is an important therapeutic goal. Desmopressin can be given parenterally, intranasally, or orally and is the treatment of choice for central diabetes insipidus. In the nephrogenic disorder, the underlying cause should be eliminated; in addition, thiazide diuretics, which enhance sodium excretion, should be prescribed and an adequate fluid intake assured.

Syndrome of Inappropriate Antidiuretic Hormone Secretion

Diagnosis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) depends on the demonstration of decreased effective plasma osmolality, increased urinary osmolality, increased urinary sodium excretion (with normal salt and water intake), euvolemia, normal adrenal and thyroid function, and absence of recent diuretic therapy. Neurologic manifestations of SIADH are those of hyponatremia including encephalopathy and seizures, when the electrolyte disturbance is severe or acute. Milder degrees of hyponatremia impair performance on tests of attention and may predispose patients to falls and fractures. Neurologic causes of SIADH include head trauma, neurosurgery, brain tumor, CNS infection, stroke, hydrocephalus, and acute intermittent porphyria. Ectopic ADH production may occur from systemic malignancies or in association with pulmonary disease. Among the many drugs associated with SIADH are carbamazepine, antidepressants, neuroleptics, antineoplastic agents, and thiazide diuretics. The causes of SIADH are summarized in Table 20-6.

Osmotic demyelination syndrome, a rare but often devastating cerebral disorder associated with rapid correction of hyponatremia of any cause, has helped inform the optimal management of SIADH and other hyponatremic states. Fluid restriction and treatment of the underlying cause are mainstays of therapy, but patient adherence with the former is usually poor. Hypertonic saline and diuretics such as furosemide may be necessary for patients with seizures or those who are otherwise severely symptomatic. Demeclocycline, which induces nephrogenic diabetes insipidus, is occasionally used. More recently, vasopressin receptor antagonists (the "vaptans") are available and are under investigation as second-line treatment for SIADH.

Cerebral salt wasting, occurring in the setting of intracranial disease, is defined as hyponatremia resulting from renal sodium loss. It causes hypovolemia, in contrast to the euvolemia of SIADH, from which it must be distinguished. Rational management consists of water and sodium repletion, rather than fluid restriction, as is standard in SIADH. There are a number of unsettled issues relating to cerebral salt wasting including the difficulty of accurately determining volume status, the frequency with which the syndrome occurs, the necessity for the presence of co-existing cerebral disease, and whether it properly should be renamed renal salt wasting.

TABLE 20-6 ■ Causes of the Syndrome of Inappropriate ADH Secretion

Neurologic Disease
Head trauma or neurosurgery
Stroke
Cerebral infection: meningitis, encephalitis, brain abscess
Brain tumors
Others: hydrocephalus, delirium tremens, acute intermittent porphyria, Guillain–Barré syndrome
Pulmonary Disease
Infection: pneumonia, tuberculosis, empyema
Acute respiratory failure
Others: asthma, cystic fibrosis, pneumothorax, positive-pressure ventilation
Drugs
Psychotropic agents: antipsychotics, antidepressants
Chemotherapy: vinca alkaloids, cyclophosphamide, ifosfamide
Hormones: vasopressin, desmopressin, oxytocin
Others: carbamazepine, clofibrate, amiloride, thiazides
Neoplastic Ectopic ADH Production
Carcinoma: nasopharyngeal, bronchogenic, duodenal, pancreatic, endometrial, prostatic
Others: thymoma, lymphoma, mesothelioma, Ewing sarcoma
Other
Surgery
AIDS
Prolonged exercise

ADH, antidiuretic hormone; AIDS, acquired immunodeficiency syndrome.

Hypopituitarism

Hypothalamic and intrinsic pituitary disorders may lead to impaired secretion of anterior or posterior pituitary hormones (Table 20-7). Because prolactin, unlike other anterior pituitary hormones, is primarily regulated by inhibition, large mass lesions or other processes that disrupt the pituitary stalk can elevate prolactin levels. Prolactin levels in the resulting "stalk syndrome" will be elevated, but not to levels seen with prolactinomas. Pituitary adenomas, even when large, usually spare posterior pituitary function. Thus, the triad of diabetes insipidus, hyperprolactinemia, and deficiency of one or more anterior pituitary hormones suggests hypothalamic dysfunction or disruption of the hypothalamic–pituitary stalk.

Hypopituitarism spans a broad clinical spectrum from the acute crisis of pituitary apoplexy to the indolent and easily missed fatigue, decreased sexual interest and function, loss of body hair, and cold intolerance of a nonsecreting adenoma that has grown large enough to cause deficiencies of multiple hormones. GH deficiency causes growth failure in children and accelerated atherosclerosis and osteoporosis in adults. Hypoadrenalism due to ACTH deficiency is usually less severe than in intrinsic adrenal disease, owing to preserved mineralocorticoid secretion. Gonadotropin deficiency causes loss of libido and impotence. Thyroid dysfunction resulting from TSH deficiency is generally less severe than primary

TABLE 20-7 ■ Differential Diagnosis of Hypopituitarism

Neoplasm
Pituitary macroadenoma
Other sellar region tumors: craniopharyngioma, meningioma, glioma, chondroma, chordoma, metastases
Trauma
Head injury or neurosurgery
Radiotherapy
Stalk section
Vascular
Pituitary hemorrhage or infarction
Subarachnoid hemorrhage
Stroke
Inflammatory
Infection: meningitis, encephalitis, abscess
Granulomatous disorders
Lymphocytic hypophysitis
Other autoimmune disorders
Infiltrative
Hemochromatosis
Amyloidosis
Empty Sella Syndrome
Developmental
Septo-optic dysplasia
Pituitary aplasia

hypothyroidism. Neuropsychiatric abnormalities and myopathic weakness are features of hypothyroidism and hypocortisolism.

Pituitary tumors or the consequences of their treatment account for some cases of hypopituitarism. Hypopituitarism exceeds 25 percent after traumatic brain injury and has been associated with cognitive impairment, metabolic abnormalities, and reduced quality of life.

PARATHYROID GLANDS

The two pairs of parathyroid glands lie behind the thyroid, secreting parathyroid hormone (PTH). PTH increases serum calcium through direct effects on kidney and bone as well as by indirect effects on gastrointestinal absorption. PTH secretion, in turn, is regulated by ionized calcium concentration in extracellular fluid. The C cells of the thyroid secrete calcitonin, which inhibits bone resorption, thus opposing PTH activity and lowering serum calcium levels. Vitamin D and its metabolites also influence absorption of calcium and other minerals and are sometimes used to treat parathyroid disorders.

Primary Hyperparathyroidism

Primary hyperparathyroidism most commonly results from PTH oversecretion by a solitary parathyroid adenoma and is a common cause of hypercalcemia.[13] Primary hyperparathyroidism is not rare, and the diagnosis is frequently made in patients with few or no symptoms. The classic triad of nephrolithiasis, osteitis, and peptic ulcer disease (“stones, bones, and abdominal groans”) characteristic of advanced primary hyperparathyroidism, is rarely seen today.

Common symptoms include fatigue and subjective weakness, although diverse central and peripheral nervous system syndromes have been reported. Neuropsychiatric syndromes include impaired memory, personality changes, affective disorders, delirium, and psychosis. Elderly patients may be particularly vulnerable. The association of hyperparathyroidism with cognitive disorders remains controversial. The degree of hypercalcemia does not always correlate with clinical severity, although neurologic manifestations typically improve with treatment of the endocrine disorder. Parkinsonism and a syndrome resembling motor neuron disease, reversing with parathyroid surgery, have been described. Myelopathy has been reported from compression by “brown tumors” seen in osteitis fibrosa cystica or on a presumed metabolic basis with normal spine MRI. Neuromuscular symptoms include proximal weakness, muscle pain and stiffness, and paresthesias and typically respond to parathyroidectomy.

Hypercalcemia, usually with concomitant hypophosphatemia, and elevated levels of immunoreactive PTH suggest the diagnosis. Distinguishing malignancy-associated hypercalcemia, with or without ectopic PTH secretion, from primary hyperparathyroidism can be challenging. Parathyroidectomy relieves symptoms and normalizes serum calcium levels in mild as well as severe disease. In patients with mild symptoms or those who are not surgical candidates, cinacalcet and bisphosphonates are options.

Hypoparathyroidism

Hypoparathyroidism results from decreased PTH secretion, causing hypocalcemia. PTH deficiency occurs most commonly after thyroidectomy or other neck surgery, including parathyroidectomy.[14] Hypoparathyroidism may also develop as a feature of autoimmune endocrinopathies and inherited disorders such as Kearns–Sayre syndrome and DiGeorge syndrome. Other causes include glandular destruction from infiltrative processes or radiation. Severe magnesium depletion impairs both PTH secretion and its peripheral action. PTH resistance, referred to as pseudohypoparathyroidism, may develop as a consequence of circulating antagonists, abnormal receptors, or defects in receptor-linked enzyme activity.

Diverse central and peripheral nervous system disorders may occur, primarily owing to hypocalcemia. Dementia and psychosis have been described, with varying degrees of improvement after correction of serum calcium concentration. Seizures, usually generalized, may occur and, because their response to antiepileptic drugs is often unsatisfactory, are best managed by correction of serum calcium. Intracranial calcification, most commonly in the basal ganglia and cerebellum, develops in many hypoparathyroid patients, most of whom are asymptomatic. Diverse extrapyramidal syndromes, with or without associated intracranial calcification, have been described including parkinsonism, choreoathetosis, hemiballismus, and torticollis. Further discussion is provided in Chapter 58. Tetany is the classic peripheral nervous system manifestation of hypocalcemia and may be difficult to distinguish from seizures. Findings on examination include Trousseau and Chvostek signs and carpopedal spasm. Clinically significant autonomic dysfunction is rare; the electrocardiogram may demonstrate a prolonged QT interval. Less common neurologic syndromes include myopathy, peripheral neuropathy, sensorineural hearing loss, and intracranial hypertension.

ADRENAL GLANDS

The paired adrenal glands, situated atop the kidneys, consist of the medulla, derived from neuroectoderm, and the cortex, derived from mesoderm. Their distinct embryologic origins parallel their different endocrine functions. Adrenal medullary chromaffin cells secrete catecholamines, principally epinephrine, regulated by cholinergic preganglionic sympathetic neurons. Adrenal cortical cells secrete sex hormones, corticosteroids, and mineralocorticoids regulated by the hormones ACTH and angiotensin II. This complex neural, endocrine, and metabolic integration allows the adrenal gland to fulfill its critical role in coordinating energy homeostasis and stress responses.

Adrenal Cortex

PRIMARY ALDOSTERONISM

Aldosterone, the major mineralocorticoid in humans, promotes sodium retention and potassium excretion and is primarily controlled by the renin-angiotensin system. In primary aldosteronism, hormone production is inappropriately elevated, most commonly from bilateral adrenal hyperplasia or an aldosterone-secreting adenoma. The resulting volume expansion causes hypertension, which may be treatment-resistant. Hypokalemic alkalosis is a useful clue to the diagnosis when present and when severe can lead to muscle weakness, paresthesias, tetany, or paralysis. The association of hypokalemia and refractory hypertension in ischemic or hemorrhagic strokes should prompt an assessment of the renin-angiotensin system to rule out primary aldosteronism.

CUSHING SYNDROME

Although Cushing disease refers specifically to excess circulating corticosteroids induced by an ACTH-secreting pituitary adenoma, Cushing syndrome is a more general term for hypercortisolism and its associated clinical features, regardless of whether steroid excess is exogenous or endogenous. Corticosteroid treatment for neurologic disorders is usually parenteral or oral, and clinicians are familiar with the importance of monitoring for medical and neurologic complications.

In patients with suspected Cushing syndrome who are not taking corticosteroids, diagnosis is directed toward demonstrating hypercortisolism and defining the source of corticosteroid excess beginning with the same screening tests as for Cushing disease, followed by additional confirmatory blood tests and imaging. ACTH-dependent causes of hypercortisolism are the most common endogenous form and include Cushing disease.

TABLE 20-8 ■ Differential Diagnosis of Hypercortisolism

Non-Cushing Hypercortisolemia
Obesity
Major depression
Alcoholism
Pregnancy
Glucocorticoid resistance
Diabetes mellitus
Others (usually without clinical features of Cushing syndrome): acute illness, malnutrition, elevated cortisol-binding globulin
Exogenous
Corticosteroid or ACTH administration
Endogenous
ACTH-dependent
Pituitary ACTH production (Cushing disease) Ectopic ACTH production: carcinoid or other neuroendocrine tumors Ectopic CRH syndrome
ACTH-independent
Adrenal adenoma or carcinoma Adrenal macronodular hyperplasia McCune–Albright syndrome

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

Adrenal lesions such as hyperplasia, adenoma, or carcinoma account for many of the ACTH-independent forms. The differential diagnosis of hypercortisolism is outlined in Table 20-8. Treatment depends on the specific underlying cause and may include steroidogenic inhibitors.

ADRENAL INSUFFICIENCY

With exogenous corticosteroids responsible for many cases of hypercortisolism, it is not surprising that rapid withdrawal of these agents is a common cause of adrenal insufficiency. Acute adrenal failure may be fatal and should be considered in patients with unexplained hypotension. When adrenal insufficiency develops more gradually, systemic manifestations include fatigue, weight loss, loss of libido, hypotension, nausea, vomiting, dry skin, loss of axillary and pubic hair, and limb pain.[15] The low specificity of these symptoms and lower frequency of more specific symptoms such as salt craving and hyperpigmentation mean that diagnosis of adrenal insufficiency is often delayed. Cerebral symptoms include apathy, depression, confusion, and, occasionally, paranoia and psychosis. Myalgias, myopathic weakness, cramping, and hyperkalemic periodic paralysis may develop occasionally.

TABLE 20-9 ■ Causes of Adrenal Insufficiency

Primary (Addison disease)
Autoimmune adrenalitis
Infection: meningococcemia, tuberculosis, cytomegalovirus
Metastases
Adrenal infarction or hemorrhage
Adrenoleukodystrophy and other inherited disorders
Drugs: steroidogenesis inhibitors
Secondary
Corticosteroid administration
Pituitary disease or surgery

Primary adrenal insufficiency, or Addison disease, results from glandular dysfunction or destruction, acutely or chronically, by hemorrhage, infection, autoimmune disorders, surgery, metastases, steroidogenesis inhibitors, or hereditary disorders.

Inherited causes with their own neurologic features include adrenomyeloneuropathy and adrenoleukodystrophy, which are X-linked disorders characterized by accumulation of very-long-chain fatty acids. Adrenal disease may antedate neurologic symptoms or occur in isolation, and the diagnosis should be considered in young men with Addison disease.

Secondary adrenal insufficiency results from ACTH deficiency, due to hypothalamic or pituitary lesions, surgery, or suppression of the hypothalamic–pituitary–adrenal axis by exogenous corticosteroids. The differential diagnosis of adrenal insufficiency is outlined in Table 20-9.

The basal morning cortisol and synthetic corticotropin stimulation test usually constitute the initial steps in evaluating suspected adrenal insufficiency. Steroid replacement is lifesaving in acute adrenal failure and relieves symptoms in chronic states.

Adrenal Medulla

PHEOCHROMOCYTOMA AND NEUROENDOCRINE TUMORS

Pheochromocytoma is a rare catecholamine-secreting tumor that arises from adrenal chromaffin cells. Most are sporadic, but pheochromocytomas also occur as a part of inherited disorders, including neurofibromatosis type 1 and von Hippel–Lindau disease. Extra-adrenal chromaffin cell tumors ("paragangliomas") are typically nonsecretory when they occur in the head and neck and occasionally cause cranial neuropathies. More commonly, paragangliomas occur along the sympathetic chain and secrete catecholamines, with clinical features similar to pheochromocytoma. A classic cause of secondary hypertension, these tumors also present with paroxysmal headache, diaphoresis, anxiety, tremor, dizziness, or flushing, in varying combinations. They may also present acutely, with ischemic or hemorrhagic stroke, reversible cerebral vasoconstriction syndrome, seizure, or delirium. Included in the extensive differential diagnosis are anxiety disorders, panic attacks, migraine, hyperthyroidism, menopausal symptoms, effects of sympathomimetic drugs, and dysautonomia. Recommended initial testing for pheochromocytoma or paraganglioma is measurement of urine or plasma fractionated metanephrines, with phlebotomy performed supine and with additional restrictions on antecedent smoking, caffeine intake, and exercise. CT or MRI, increasingly supplemented with functional imaging, localize the tumor, which is usually managed surgically.

Other neuroendocrine tumors may cause neurologic symptoms related to secretion of other biogenic amines or peptides. Flushing, which may raise concern for dysautonomia, is a feature of carcinoid tumors—neoplasms of the gastrointestinal tract or lung which secrete serotonin, dopamine, prostaglandins, and other molecules. Pancreatic neuroendocrine tumors may secrete insulin, causing hypoglycemic symptoms; GHRH, causing acromegaly; or ACTH, causing Cushing syndrome.

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SECTION

5

Cutaneous Disorders

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CHAPTER 21

The Skin and Neurologic Disease

OREST HURKO

TUMORS
- Neurofibromatosis Type I
- Neurofibromatosis Type II
- Tuberous Sclerosis
- Melanoma

STROKE
- Fabry Disease
- Hereditary Hemorrhagic Telangiectasia
- Homocystinuria
- Endocarditis
- Antiphospholipid Syndrome
- Takayasu Arteritis

MENINGITIS AND MENINGOENCEPHALITIS
- Meningococcal Meningitis
- Lyme Borreliosis
- Syphilis
- Sarcoidosis
- Behçet Disease

INTERMITTENT ENCEPHALOPATHIES
- Systemic Lupus Erythematosus
- Thrombotic Thrombocytopenic Purpura
- Porphyria

DEMENTIA
- HIV-AIDS
- Cockayne Syndrome

SEIZURE DISORDERS
- Sturge—Weber Syndrome
- Incontinentia Pigmenti (Bloch—Sulzberger Disease)
- Linear Sebaceous Nevus Syndrome

ATAXIA
- Ataxia Telangiectasia
- Cerebrotendinous Xanthomatosis
- Classic Refsum Disease
- Hartnup Disease and Related Disorders

MYELOPATHY
- Rheumatoid Arthritis
- Sjögren Syndrome

PERIPHERAL NEUROPATHY
- Leprosy
- Systemic Sclerosis
- Systemic Vasculitis

MYOPATHY
- Dermatomyositis

This chapter provides an overview of disorders that have both neurologic and cutaneous manifestations, the latter often reducing what would have been a broad differential diagnosis into a single entity. Because the emphasis is on diagnosis by a neurologist, the presentation is organized around familiar neurologic syndromes rather than pathologic or dermatologic entities. This approach is complementary to those based on traditional pathophysiologic categories, such as genetic, autoimmune, and infectious disorders. Patients present to the neurologist with signs and symptoms, not with biopsies.

Usually a disease cannot be related to either a single cutaneous sign or a single neurologic syndrome. With a goal of minimal repetition but a comprehensive presentation, the text is limited to important representative diseases. Each is described only once, grouped with its most characteristic clinical presentation where possible. Secondary manifestations are mentioned in passing or in tables. Details are necessarily limited, but are supplemented with more comprehensive tables and, where applicable, annotation with the code number in the continuously updated Online Mendelian Inheritance in Man (OMIM).[1] The discussion is limited to disorders that permit survival to adulthood.

TUMORS

Earlier classifications of neurocutaneous disorders described phakomatoses, disorders that were thought

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to affect exclusively structures arising from the embryonic ectoderm: the skin, eyes, and nervous system. This designation was originally applied to two autosomal dominant disorders associated with tumors: neurofibromatosis type I and tuberous sclerosis.[2] However, the category gradually expanded to encompass a wide variety of other neurologic disorders, including Sturge–Weber syndrome, which is not associated with tumors, and von Hippel–Lindau syndrome, associated with tumors but not with cutaneous lesions. Furthermore, many of these disorders involved tissues with mesodermal and endodermal origins as well. Phakomatosis has outlived its utility as a diagnostic category.

Numerous disorders are associated with tumors, cutaneous manifestations, and neurologic disease. In many cases the tumors themselves are responsible for the cutaneous or neurologic symptoms, but in others they are independent manifestations of a more complex syndrome.

Neurofibromatosis Type I

Neurofibromatosis type I (NF1; von Recklinghausen disease), an autosomal dominant disorder (OMIM 162200), is characterized by café-au-lait spots, fibromatous dermal tumors, and Lisch nodules of the iris as well as neoplasms of both the peripheral and the central nervous system (CNS). The earlier designation as peripheral neurofibromatosis (strictly speaking, a misnomer) served to distinguish this disorder from the genetically and clinically distinct central neurofibromatosis, now neurofibromatosis type II (NF2; OMIM 101000), as well as schwannomatosis 1 (SWNTS1, OMIM 162091) and 2 (SWNTS1, OMIM 615670).

NF1 is the most common single-gene disorder of the nervous system, affecting 1 in 3,500 individuals. It results from heterozygosity for a mutant form of a large gene on chromosome 17q11.2 that encodes a cytoplasmic protein with multiple regulatory functions. The NIH consensus criteria permit unequivocal diagnosis of NF1 even without demonstration of the genetic mutation, by clinical observation of at least two of the following: (1) the presence of six or more café-au-lait macules with a diameter of ≥ 5 mm in children younger than 6 years and ≥ 15 mm in older people (Fig. 21-1); (2) two or more neurofibromas of any type or one plexiform neurofibroma; (3) axillary or inguinal region freckling; (4) optic pathway glioma; (5) two or more Lisch nodules (whitish tumors of the iris); (6) dysplasia of the sphenoid bone or thinning of the cortex of long bones with or without pseudarthrosis; and/or (7) a first-degree relative exhibiting these changes.

The familiar café-au-lait spots are present at birth, as are plexiform neurofibromas and focal bone dysplasias, but axillary freckling, optic gliomas, Lisch nodules, and neurofibromas appear later in childhood. Of these, axillary freckling is the most diagnostically reliable, being present in all individuals with NF1 by the end of puberty. Café-au-lait spots alone are not diagnostic of NF1 because fewer than five spots are found frequently in individuals who are well. Café-au-lait spots as an isolated trait can be transmitted as an autosomal dominant (OMIM 114030) or as occasional features in other heritable disorders including tuberous sclerosis, the microcephalic disorders Nijmegen breakage syndrome (ataxia telangiectasia variant VI, OMIM 251260), X-linked Russell–Silver syndrome (OMIM 312780), Turcot mismatch repair cancer syndrome (OMIM

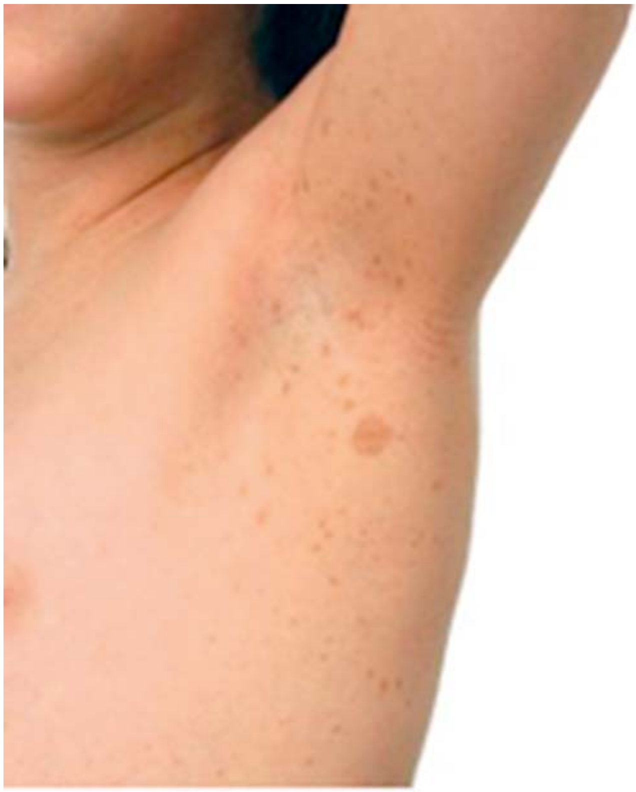

FIGURE 21-1 ■ Neurofibromatosis type I: axillary freckling—a cluster of freckle-sized café-au-lait macules. (From Kurlemann G: Neurocutaneous syndromes. Handb Clin Neurol 108:513, 2012, with permission.)

276300; polyposis coli, rhabdomyosarcomas, medulloblastomas, ependymomas and other gliomas), the rare Westerhof growth retardation syndrome (OMIM 154000), and perhaps most famously in McCune–Albright polyostotic fibrous dysplasia (OMIM 174800). The old clinical pearl that the rough border of McCune–Albright café-au-lait spots distinguishes them from the smooth borders seen in NF1 is not reliable.

Malignant neoplasms or benign tumors of the nervous system occur in 45 percent of individuals with NF1. Optic nerve gliomas develop in 15 percent. However, neurologic involvement most often results from benign neurofibromas in the root entry zone of peripheral nerves, causing radiculopathy or compression of the spinal cord. Plexiform neurofibromas, which can be nodular or diffuse, arise from nerve trunks. Diffuse plexiform neurofibromas are usually congenital and undergo transformation in about 4 percent of cases into malignant peripheral nerve sheath tumors that are severely painful, tender, and hard. The more common dermal neurofibromas are usually innocent, permitting conservative management in asymptomatic people. The incidence of non-neural tumors is also increased modestly, especially rhabdomyosarcomas of the urogenital tract and myelogenous leukemia.

In addition, there are neurologic sequelae not related to tumors. The most significant of these are poorly characterized T2 hyperintensities in the centrum semiovale (unidentified bright objects), the density of which correlates with mild cognitive impairment. In addition to these neurologic, ocular, and cutaneous manifestations, there may also be cardiovascular, gastrointestinal, and orthopedic manifestations.

Neurofibromatosis Type II

This genetically distinct autosomal dominant disorder (OMIM 101000; also known as NF2, bilateral acoustic neurofibromatosis, or BANF) is characterized by tumors of the eighth cranial nerve in the cerebellopontine angle, meningiomas, and schwannomas of the dorsal roots of the spinal cord. It is less common than NF1 by an order of magnitude, affecting 1 in 25,000 live births in association with heterozygosity for a mutant form of merlin, a critical regulator of cell–cell adhesion, transmembrane signaling, the actin cytoskeleton, and resultant inhibition of proliferation. It is encoded on chromosome 8. Other mutations of this gene result in a clinically related but distinct Mendelian disorder, congenital cutaneous schwannomatosis 1 (OMIM 162091) or in some familial predispositions to meningiomas (OMIM 607174). Typically, NF2 presents in young adults, but hearing loss has been reported as early as age 6. Proposed diagnostic criteria for definite NF2 are bilateral vestibular schwannomas; or a family history of NF2 in one or more first-degree relatives plus (1) unilateral vestibular schwannomas at age less than 30 years, or (2) any two of the following: meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract. Bilateral acoustic neuromas occur in less than 5 percent of most series. The cutaneous manifestations are also distinct from that of NF1. Café-au-lait spots are present in about 40 percent of individuals, but only about 1 percent have six, the minimum seen in NF1. There are three types of cutaneous tumors: (1) discrete well-circumscribed, slightly raised, roughened areas of skin often pigmented and accompanied by excess hair, which are seen in about one-half of affected individuals; (2) subcutaneous well-circumscribed, nodular tumors located on peripheral nerves seen in about one-third; and (3) violaceous papillary skin neurofibromas, similar to those seen in NF1, in about one-fifth. One-third of NF2 patients have no cutaneous lesions.

Tuberous Sclerosis

This autosomal dominant neurocutaneous disorder was originally described as a phakomatosis, as had been NF1. It is characterized by hamartomas in multiple organ systems, including the brain, skin, heart, kidneys, and lung. The characteristic brain lesions, named tubers because of their fancied resemblance to potatoes, are benign, but some 5 to 15 percent of affected individuals also develop malignant brain neoplasms, most frequently subependymal giant cell astrocytomas. These often develop at the foramen of Monro or elsewhere on the wall of the lateral ventricle or the retina. More frequent neurologic presentations are learning difficulties, behavioral problems, autism, or epilepsy, often the severe West syndrome. The characteristic skin lesions are pale "ash leaf spots," present in 90 percent of affected individuals. These are difficult to spot on light-skinned individuals unless examined with an ultraviolet Wood light (Fig. 21-2). Such an examination will also facilitate the recognition of smaller confetti-like

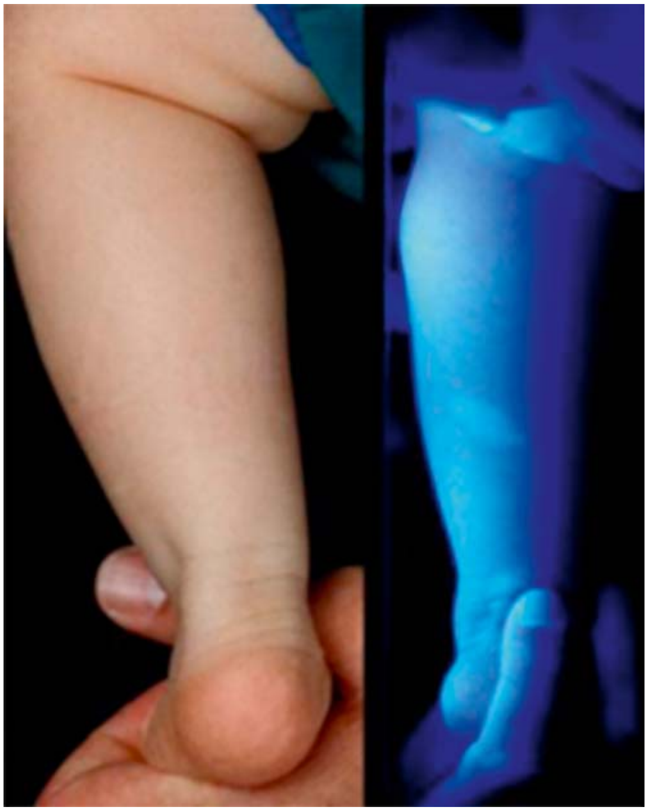

FIGURE 21-2 ■ Tuberous sclerosis: ash leaf spot in Wood light. (From Kurlemann G: Neurocutaneous syndromes. Handb Clin Neurol 108:513, 2012, with permission.)

hypopigmented patches that are present in about one-third of patients, but only rarely in normal individuals. In addition to these flat hypopigmented lesions and occasional café-au-lait spots, there are three kinds of distinctive raised cutaneous lesions: shagreen patches (Fig. 21-3), periungual fibromas (Fig. 21-4), and facial angiofibromas. The latter can be mistaken for acne on casual inspection. There are also systemic manifestations: usually asymptomatic cardiac rhabdomyomas, present at birth and regressing in childhood, but sometimes associated with arrhythmias; renal cysts, angiolipomas, and carcinomas; and pulmonary lymphangioleiomyomas.

Tuberous sclerosis (TSc) can result from mutation of either of two genes. About 70 percent of cases (TSc 2, OMIM 613254) result from heterozygous mutation of tuberin encoded on chromosome 16p13.3, the remainder (TSc 1, OMIM 191100) from mutations of the gene encoding hamartin on chromosome 9q34.13. Unlike the case for the phenotypically distinct NF1 and NF2, each of which results from disruption of either of two independent, noninteracting proteins, TSc 1 and TSc 2 are practically indistinguishable clinically. This is as would be predicted by the known interaction of hamartin and tuberin to form a single complex, the activity of which is disrupted by mutation of either subunit.

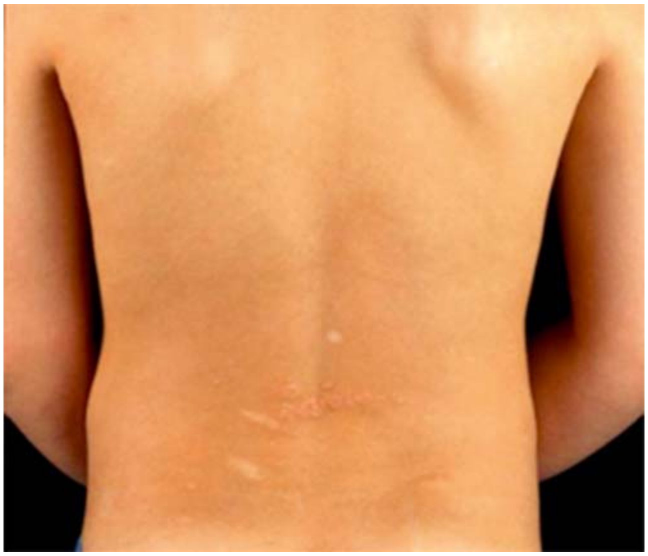

FIGURE 21-3 ■ Tuberous sclerosis: ash leaf spot and shagreen patch. (From Kurlemann G: Neurocutaneous syndromes. Handb Clin Neurol 108:513, 2012, with permission.)

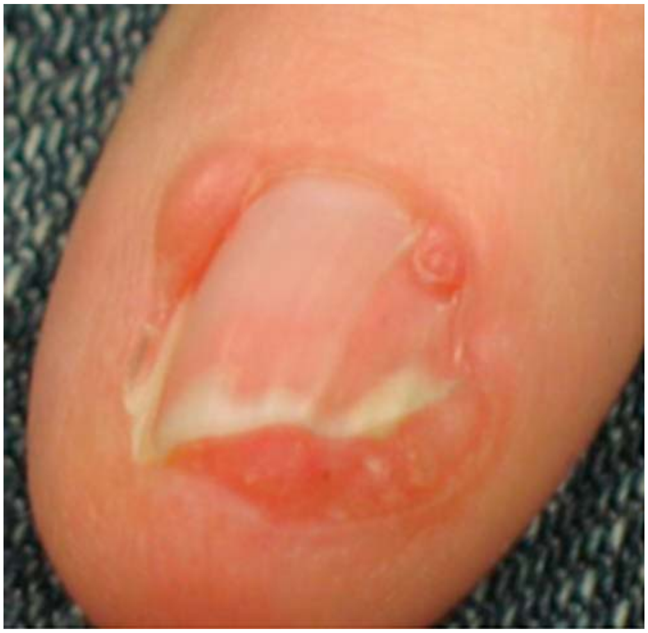

FIGURE 21-4 ■ Tuberous sclerosis: nail-fold fibroma. (From Kurlemann G: Neurocutaneous syndromes. Handb Clin Neurol 108:513, 2012.)

This complex regulates the activity of the downstream pathway of the mammalian target of rapamycin (mTOR), which is disrupted by mutation in another neurocutaneous disorder, the Cowden multiple hamartoma syndrome (OMIM 158350).

Melanoma

Melanoma is the most lethal of skin cancers, largely because of its propensity for early and highly neurotropic metastasis.[3] In most instances, involvement of the nervous system by melanoma is by metastasis from a primary cutaneous lesion first to a local regional lymph node, then to the lung whence it metastasizes further to brain, bone, or liver. Unlike the usual solitary brain metastases from more common primaries such as lung, breast, and kidney, brain metastases of melanoma are characteristically multiple. The other two types of primary cutaneous neoplasms, the more common basal cell carcinoma and the more invasive squamous cell carcinoma, do not metastasize to the brain.

Furthermore, tumors of the nervous system (including gliomas, medulloblastomas, ependymomas, meningiomas, and acoustic neurilemmomas) have an increased likelihood as secondary tumors in patients with cutaneous melanoma as well as in their family members. The molecular bases underlying these associations are only partially understood.

An increased incidence of cutaneous melanomas is seen in a more complex heritable neurocutaneous syndrome, xeroderma pigmentosa (OMIM 610651). This autosomal recessive disorder is characterized by increased sensitivity to sunlight as well as widespread neurologic involvement. Signs include microcephaly, mental retardation, ataxia, ventriculomegaly, cerebellar atrophy, basal ganglia calcification, and disordered central and peripheral myelination.

In addition to those syndromes in which melanoma originates in the skin, there is also the rare neurocutaneous melanosis (OMIM 249400), in which there is a primary melanoma of the CNS in over 50 percent of cases, but no malignant melanoma in the periphery. In this disorder there are large multiple pigmented skin nevi (> 20 cm) (Fig. 21-5), as well as cranial nerve palsies from histologically benign melanocytic invasion of the meninges, Dandy–Walker malformation, and suprasellar calcifications. Death usually occurs in childhood.

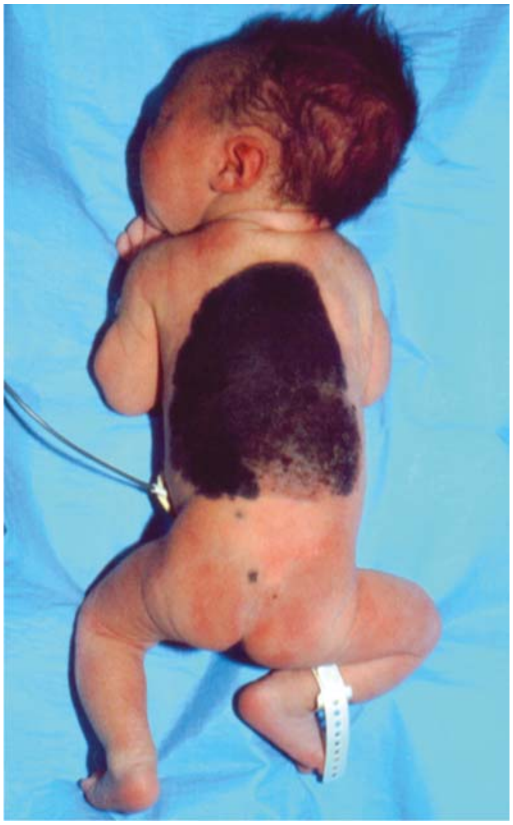

FIGURE 21-5 ■ Neurocutaneous melanosis. (From Jones, K: Smith's Recognizable Patterns of Human Malformation. Saunders, Philadelphia, 2005, with permission.)

STROKE

A number of neurocutaneous disorders are associated with either ischemic or hemorrhagic stroke, or both. The underlying mechanisms range from intrinsic vascular disease to cardiac or paradoxical embolization and to coagulopathies or platelet disorders, as summarized in Table 21-1.

Fabry Disease

Fabry disease is an X-linked neurocutaneous disorder (OMIM 301500) characterized by stroke, peripheral neuropathy, and progressive renal and cardiac failure. These sequelae occur both in hemizygous males as well as in heterozygous females, albeit later and usually, but not invariably, with less severity. A pathognomonic whorl-like corneal dystrophy is seen with equal severity in both sexes. Affected males are easily recognized by a purpuric skin rash: discrete angiokeratoma, most prevalent between the knees and nipples. Females,

TABLE 21-1 ■ Ischemic or Hemorrhagic Stroke with Cutaneous Manifestations

Disease	Cutaneous Lesions	Neurologic Features
Antiphospholipid syndrome	Livedo reticularis	Ischemic stroke, chorea, neuropsychiatric symptoms, relapsing-remitting central vasculitis, myelopathy
Behçet disease	Erythema nodosum, genital and oral aphthous ulcers	Brainstem meningoencephalitis, dural sinus thrombosis, ischemic stroke, peripheral neuropathy (rare)
Bone fragility with contractures, arterial rupture, and deafness (OMIM 612394)	Ecchymoses, blistering of fingers, toes, pinnae	Cerebral hemorrhage, developmental delay
Cerebral cavernous malformations; CCM (OMIM 116860, 603284)	Angiomas, hyperkeratotic cutaneous vascular lesions	Small, localized intracranial hemorrhages
Diabetes mellitus	Necrobiosis lipoidica diabeticorum, poorly healing ulcers	Lacunar stroke, peripheral neuropathy, retinopathy, metabolic coma
Endocarditis	Petechiae, Janeway lesions, Osler nodes, splinter hemorrhages	Septic embolic strokes
Fabry disease (OMIM 301500)	Angiokeratoma starting at the umbilicus and knees, spreading to buttocks and scrotum	Ischemic stroke, seizures, peripheral neuropathy, autonomic dysfunction, acral paresthesias, painful crises
Factor XIII subunit A deficiency (OMIM 613225)	Ecchymoses	Intracranial hemorrhage
Glanzmann thrombasthenia (OMIM 273800)	Easy bruisability, purpura	Intracranial hemorrhage
Hemolytic-uremic syndrome (OMIM 235400)	Erythematous necrotic skin lesions	Seizures, coma, hemiparesis, cognitive defects, visual defects, dysphasia
Hereditary hemorrhagic telangiectasia of Osler—Weber—Rendu (OMIM 187300, 600376, 601101, 610655)	Telangiectasia	Ischemic and hemorrhagic stroke
Homocystinuria due to cystathionine β-synthase deficiency (OMIM 236200)	Malar flush, livedo reticularis, hypopigmentation	Ischemic stroke, seizures, mental retardation, psychiatric disorders, depression, personality disorder
Familial hypercholesterolemia (OMIM 143890)	Xanthomas, xanthelasma	Ischemic thromboembolic stroke
Hereditary neurocutaneous angiomas (OMIM 106070)	Large irregular flat hemangiomas	Spinal angiomas and cerebral thin-walled angiomas
Hyper-IgE recurrent infection syndrome, autosomal recessive (OMIM 243700)	Severe eczema, atopic dermatitis, recurrent skin abscesses	Ischemic infarctions, subarachnoid hemorrhage
Malignant atrophic papulosis (OMIM 602248)	Multiple asymptomatic papules with atrophic white centers surrounded by telangiectatic lesions	Ischemic infarctions
Prothrombin deficiency, congenital (OMIM 613679)	Ecchymoses, easy bruising	Intracranial hemorrhage
Pseudoxanthoma elasticum (OMIM 264800)	Pseudoxanthoma, multiple papules, peau d'orange, angioid streaks, subcutaneous calcification usually in blood vessels	Stroke, retinopathy
Pseudoxanthoma elasticum, forme fruste (OMIM 177850)	Small, yellow papules, peau d'orange, elastosis perforans serpiginosa	Cerebral hemorrhage, retinopathy
Schimke-type immuno-osseous dysplasia (OMIM 242900)	Hyperpigmented macules	Moyamoya, cerebral infarctions

(Continued)

TABLE 21-1 ■ (Continued)

Disease	Cutaneous Lesions	Neurologic Features
Systemic lupus erythematosus	Photosensitivity, malar rash, telangiectasia, discoid lupus, patchy alopecia, mucosal ulcers, angioneurotic edema, Raynaud phenomenon, subcutaneous nodules, palpable purpura, gangrene, erythema multiforme	Ischemic and hemorrhagic stroke, encephalopathy, chorea, peripheral neuropathies
Takayasu arteritis	Palpable purpura	Ischemic stroke
Thrombophilia due to protein C deficiency, autosomal dominant (OMIM 176860)	Warfarin-induced skin necrosis	Cerebral thrombosis
Thrombocytopenia—absent radius syndrome (OMIM 274000)	Nevus flammeus on forehead, dysseborrheic dermatitis	Intracranial hemorrhage, absent corpus callosum, spina bifida

having two X chromosomes, are twice as likely to have the pathogenic mutation of α-galactosidase (also commonly known as ceramide trihexosidase). Nevertheless, affected female heterozygotes frequently remain undiagnosed because they rarely have the characteristic cutaneous lesions, even though they can have severe neurologic, cardiac, and renal manifestations.

Stroke is a late manifestation of the vascular deposition of lipid in Fabry disease. It was underappreciated until survival was prolonged by renal transplantation and, now, by enzyme-replacement therapy. A painful small-fiber neuropathy with autonomic dysfunction and episodic severely painful abdominal crises, reminiscent of those of the hepatic porphyrias, occurs early in the disease. Other early manifestations are small infarctions in the retina and kidneys. The latter lead to renal failure, which had previously caused death of affected hemizygotes by the third decade.

Although Fabry disease is also referred to as angiokeratoma diffusum, these skin lesions are not pathognomonic. They are also manifestations of other Mendelian neurocutaneous disorders associated with mental retardation: aspartylglucosaminuria (OMIM 208400; seizures), fucosidosis (OMIM 230000; seizures and peripheral neuropathy), lysosomal beta A mannosidosis (OMIM 248510), Ramon syndrome (OMIM 266270; a posterior cerebral leukoencephalopathy), Kanzaki disease (OMIM 609242, adult-onset mild cognitive impairment), and Bannayan—Riley—Ruvalcaba syndrome (OMIM 153480; megaencephaly, meningioma, pseudopapilledema).

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT), an autosomal dominant disorder also known eponymously as Osler—Weber—Rendu syndrome, is a vascular dysplasia that gives rise to hemorrhagic and ischemic strokes. These arise from a diverse set of peripheral as well as central vascular abnormalities, ranging from ischemic strokes and brain abscesses from paradoxical emboli passing through pulmonary venous malformations to intracerebral vessels, and subarachnoid hemorrhages from cerebral arteriovenous malformations. It is important to search for previously unsuspected pulmonary arteriovenous malformations before assuming local vascular pathology as a cause of stroke, because these pulmonary lesions can be effectively obliterated by embolization. The mucocutaneous telangiectasias for which the disorder is named are most often found on the tongue, lips, palate, fingers, face, conjunctiva, trunk, nail beds, and fingertips. Similar systemic vascular malformations are responsible for frequently problematic recurrent epistaxis, hepatic cirrhosis, and gastrointestinal hemorrhage later in life. Depending on the vascular anatomy, there may be either a polycythemia or an anemia.

This disorder is genetically heterogeneous. HHT type 1 (OMIM 187300) results from heterozygosity for a mutation of the gene on chromosome 9q34.11 encoding endoglin, a homodimeric membrane glycoprotein expressed mostly on the vascular endothelium, a component of the transforming growth factor-β receptor complex; HHT type 2 (OMIM 600376), from heterozygosity for mutation of the gene on chromosome 12q13.13 encoding activin receptor-like kinase 1; and HHT type 5 (OMIM 615506) from heterozygous mutation in the *GDF2* gene (OMIM 605120) on chromosome 10q11 encoding growth/differentiation factor 2. HHT type 3 (OMIM 601101) has been mapped to chromosome 5q31.3-q32 and HHT type 4 (OMIM 610655) to chromosome 7p14. The genes mutated in the latter two entities have not yet been identified.

Homocystinuria

Homocystinuria is a feature of several different neurologic disorders, only one of which, homocystinuria due to cystathionine β-synthase deficiency (OMIM 236200), is associated either with cutaneous lesions or with stroke. In this disorder cutaneous hypopigmentation, malar flush, and livedo reticularis are not as striking as the Marfan-like disproportionate tall stature and ectopia lentis, which provide the most evident clues to diagnosis. Neurologic features include ischemic thromboembolic strokes in about 25 percent of homozygotes, as well as mild mental retardation, seizures, and a variety of psychiatric disturbances that include personality disorders and depression. Diagnosis is critical, because over half of affected individuals respond to simple treatment with pyridoxine, vitamin B_6. Furthermore, even pyridoxine nonresponders benefit from dietary modification to reduce methionine and increase cysteine as well as supplementation with betaine.

The classic syndrome associated with homozygosity for mutations in the gene cystathionine β-synthetase is rare, but heterozygotes—encountered more commonly—are also at greater risk of ischemic stroke than the general population. Lacking the characteristic cutaneous or systemic signs, these individuals can only be detected by biochemical or genetic screening. As is always the case with rare autosomal recessive disorders, the vast majority of heterozygotes will not have an affected homozygous relative to prompt suspicion of the diagnosis.

Endocarditis

Septic emboli leading to ischemic or hemorrhagic stroke or intracranial hemorrhage from rupture of mycotic aneurysms occur in 40 percent of individuals with bacterial endocarditis.[4] In developed countries, acute endocarditis commonly occurs because of unhygienic self-administration of intravenous drugs; infections of surgically implanted artificial cardiac valves are another important cause. In the developing world, secondary infection of unrepaired congenital valvular abnormalities or those damaged by rheumatic fever are also an important contributor to infective endocarditis.

The classic cutaneous findings associated with infective endocarditis are subungual splinter hemorrhages, Janeway lesions, and Osler nodes. Splinter hemorrhages (1- to 3-mm, red to reddish-brown, longitudinal hemorrhages appearing under the nail plate) are commonly seen also as a response to repetitive trauma in otherwise healthy individuals, such as manual laborers or elderly individuals using walkers. In addition they have been reported as occasional findings in antiphospholipid syndrome, another neurocutaneous syndrome associated with stroke.

The more diagnostic Janeway lesions are nontender, large, irregular, flat macules that appear on the palms or the soles, frequently on the planar surface of a toe. These are culture-positive sites of septic emboli. In contrast, Osler nodes are tender, purple, slightly raised nodules ranging in size from 1 to 10 mm. These are typically seen on the tips or sides of toes or fingers. Unlike the Janeway lesions, they are sites of vasculitis, not embolization. Both of these lesions can appear on the thenar or hypothenar eminences.

The presence or absence of neurologic complications dictates the optimal timing of surgery for both native and prosthetic valve endocarditis, as do cardiac function and the control of the infection. In the absence of embolic events or rapidly deteriorating cardiac function, cardiac surgery is best delayed for 1 or 2 weeks of antibiotic treatment before subjecting the patient to the risks of surgery, not the least of which is cardiac bypass and attendant anticoagulation. However, if there is a stroke or transient ischemic attack, and intracranial hemorrhage has been excluded by scanning, surgery is recommended without delay.

Antiphospholipid Syndrome

The twin hallmarks of antiphospholipid antibody syndrome are either a thrombotic event, such as a stroke, or a complication of pregnancy seen in association with high titers of certain antibodies. Sometimes misleadingly referred to as lupus anticoagulants, these are thought to induce hypercoagulability by neutralizing anionic phospholipids on endothelial cells and platelets, predisposing to both arterial and venous thromboses.[5] This syndrome can be seen either as a primary abnormality or in the setting of a number of different neurocutaneous disorders: primary inflammatory diseases such as systemic lupus erythematosus, systemic sclerosis, Behçet disease, Sjögren syndrome, and rheumatoid arthritis, or infections such as syphilis, Lyme borreliosis, and human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS). In some instances, antiphospholipid syndrome has been shown to be a familial trait (OMIM 107320).

Cutaneous manifestations may be the initial clinical manifestation of the antiphospholipid syndrome. These include livedo reticularis, most commonly on the lower extremities; acrocyanosis, a Raynaud-like phenomenon; necrotizing vasculitis, with cutaneous ulceration and necrosis; erythematous macules; purpura, ecchymoses, and subungual splinter hemorrhages; and rarely, Degos malignant atrophic papulosis. The combination of livedo reticularis with multiple strokes has been designated as Sneddon syndrome. Antiphospholipid antibodies are associated with several neurologic syndromes, including stroke, transverse myelitis, and chorea. Many of these might be plausibly attributed to focal ischemia.

Takayasu Arteritis

Stroke in a young woman of Asian descent should prompt consideration of Takayasu arteritis (aortic arch syndrome or pulseless disease).[6] The differential diagnosis of aortitis includes mycotic aneurysms, syphilis, mycobacterial infections, endocarditis, as well as various autoimmune disorders, including Behçet disease, ankylosing spondylitis, sarcoidosis, and Sjögren syndrome.[7] The cutaneous manifestation of Takayasu arteritis is erythema nodosa, which occurs at an early phase in the disease. Fever and synovitis also develop prior to the large-vessel vasculopathy that defines the disorder. Neurologic involvement results from ischemic stroke from inflammation or stenosis of a proximal carotid or vertebral artery. Such strokes occur in about 20 percent of affected individuals. More commonly, involvement of the subclavian arteries leads to claudication and pulse asymmetries or frank loss of palpable pulses in the upper extremities.

The etiology of Takayasu arteritis appears to be autoimmune, with modest associations both to HLA-B52 and to elevations of serum levels of certain matrix metalloproteinases (OMIM 207600). The latter normalize after clinical improvement resulting from treatment with immunosuppressants.

MENINGITIS AND MENINGOENCEPHALITIS

A large number of disorders can present both dermatologic abnormalities and meningitis or meningoencephalitis, which can be acute, subacute, relapsing-remitting, or chronic. A few characteristic disorders are presented in detail, the others are included in Table 21-2.

Meningococcal Meningitis

Meningococcal meningitis is a fulminant disorder with a high mortality rate and serious sequelae (sensorineural hearing loss, seizures, motor deficits, hydrocephalus, cognitive abnormalities, and behavioral problems) in treated survivors. Fever, headache, and meningeal irritation develop over the course of 24 hours. The distinguishing feature of meningococcal disease is the concomitant evolution of a rapidly evolving petechial rash, usually over the trunk and lower extremities, but which can also develop on the face, mucous membranes, and arms (Fig. 21-6).[8] These cutaneous lesions can coalesce or develop into vesicles or bullae. In contrast, the cutaneous lesion associated with meningitis from infection with *Haemophilus influenzae*, previously the most common type of bacterial meningitis in children, is typically a solitary indurated area on the face, neck, upper chest, or arm. The meningococcal rash must also be distinguished from that of other disorders in Table 21-2, notably Rocky Mountain spotted fever.

In the 10 to 30 percent of cases of meningococcemia that develop too rapidly to seed the choroid plexus and meninges, the prognosis is even worse than in those cases with meningitis. Early treatment at the first recognition of the short febrile prodome and rash is critical. Although most cases of meningococcemia, either with or without meningitis, occur in children, young adults in cramped quarters, including college students and military recruits, are also at risk.

The incidence of some meningococcal infections has been reduced significantly by the introduction of a vaccine, as has the incidence of the other two most common types of acute bacterial meningitis, resulting from infection with *H. influenzae* or *Streptococcus*

TABLE 21-2 ■ Meningitis with Cutaneous Manifestations

Disorder	Cutaneous Lesions	Neurologic Features
Adams–Oliver aplasia cutis congenita type III (OMIM 614814)	Scalp defect at the vertex, cutis marmorata telangiectatica, hemangioma	Acute bacterial meningitis from scalp defect
AIDS	Seborrhea, herpes zoster, tinea corporis, *S. aureus* infection, molluscum contagiosum, Kaposi sarcoma, cryptococcosis	Transient meningitis during seroconversion
Amyloidosis V (Meretoja, Finnish) (OMIM 105120)	Cutis laxa	Cranial and peripheral neuropathies
Behçet disease	Erythema nodosum, genital and oral aphthous ulcers, papules, purpura, pustules, dermatographia, pyoderma	Chronic or recurrent meningitis, meningoencephalitis, dural sinus thrombosis
Blastomycosis	Hyperplastic granulomatous microabscesses	Rarely, chronic meningitis or cerebral abscess
Brill–Zinser epidemic typhus	Macular rash	Meningoencephalitis
Chagas disease	Romana sign, inflammation of lacrimal glands, erythema multiforme	Encephalitis
Coccidioidomycosis	Erythema nodosum, draining sinus, subcutaneous cellulitis	Meningitis common
Cryptococcosis	Macules and nodules (in 10–15% of cases)	Chronic meningitis
Haemophilus influenzae infection	Typically a single indurated area on face, neck, upper chest, or arm	Acute purulent meningitis
Histiocytic reticulosis (autosomal recessive) (OMIM 267700)	Purpura, jaundice, erythroderma	Chronic aseptic meningitis, neuropathy
Leptospirosis	Scleral conjunctival injection, maculopapular rash of trunk (in 50% of cases), jaundice	Subacute meningitis
Leukemia	Erythema nodosum, Sweet syndrome (acute febrile neutrophilic dermatosis–painful raised red plaques, commonly on face and extremities)	Meningeal leukemia is common form of relapse, especially in acute lymphocytic leukemia
Listeriosis	Generalized erythematous papules or petechiae in infants; veterinarians with tender red papules on hands	Subacute meningitis
Lyme borreliosis	Target lesion	Early aseptic meningitis, polyneuropathy, delayed demyelinating disease
Lymphoma	Erythema nodosum	Subacute meningitis, cerebral or vertebral metastases
Lymphoma, cutaneous (T cell)	Scaly erythematous patches, leonine facies, poikiloderma, hypopigmented and hyperpigmented patches with atrophy and telangiectasia	Subacute meningitis, vertebral metastases
Meningococcemia	Petechiae, usually on extremities and trunk; initially can mimic a viral exanthem	Fulminant meningitis
Murine typhus	Axillary rash, macular rash of upper abdomen, shoulders, chest	Headache, encephalopathy, and nuchal rigidity without meningitis
Neurocutaneous melanosis	Melanosis; large multiple pigmented skin nevi (>20 cm), no malignant melanoma other than CNS; primary CNS melanoma in over 50% of cases	Meningeal enhancement secondary to melanosis of pia-arachnoid, cranial nerve palsies, Dandy–Walker malformation, suprasellar calcification
Reticulosis, familial histiocytic	Purpura, jaundice, erythroderma	Chronic meningitis, peripheral neuropathy

(Continued)

TABLE 21-2 ■ (Continued)

Disorder	Cutaneous Lesions	Neurologic Features
Rocky Mountain spotted fever	Progressive rash begins on the fourth day of fever with pink macules on wrists, ankles, forearms; after 6–18 hours, on palms and soles, then centrally after 1–3 days; after 2–4 days, nonblanching petechiae	Vasculitic meningoencephalitis, choreoathetosis, deafness, hemiplegia
Sarcoidosis	Dry skin, hypohidrosis, cicatricial alopecia; *acute*: erythema nodosum, vesicles, maculopapular rash; *chronic*: lupus pernio, plaques, scars, keloids	Chronic meningitis with cranial neuropathies, peripheral neuropathy, proximal myopathy, hypothalamic involvement
Sjögren syndrome	Purpura, Raynaud phenomenon, xerostomia, candidiasis	Aseptic meningitis, sensory neuronopathy, dural sinus thrombosis
Syphilis	*Primary*: chancre. *Secondary*: maculopapular nonpruritic scaling rash (acral), patchy alopecia, condyloma lata, mucous patches, erythema multiforme, hyperpigmentation on healing, split papules, palm and sole lesions	Aseptic meningitis, late meningovascular syphilis, tabes dorsalis
Tuberculosis	Cutaneous tuberculosis is rare; primary tuberculous chancre; warty tuberculous verrucosa cutis from reinfection, postprimary lupus vulgaris, scrofuloderma, erythema nodosum, erythema multiforme	Chronic meningitis, Pott disease of vertebrae, CNS tuberculomas
Varicella zoster (chickenpox)	Vesicles with oral lesions	Meningitis with cerebellar ataxia
Vogt–Koyanagi–Harada	Vitiligo-type macules, poliosis and alopecia in convalescent third phase	Meningoencephalitis in first phase of illness, preceding uveitis
Yersinia pestis (bubonic plague)	Erythema multiforme, bubos then petechiae and ecchymoses	Meningitis can complicate all three types: bubonic, bubonic-septicemic, pneumonic

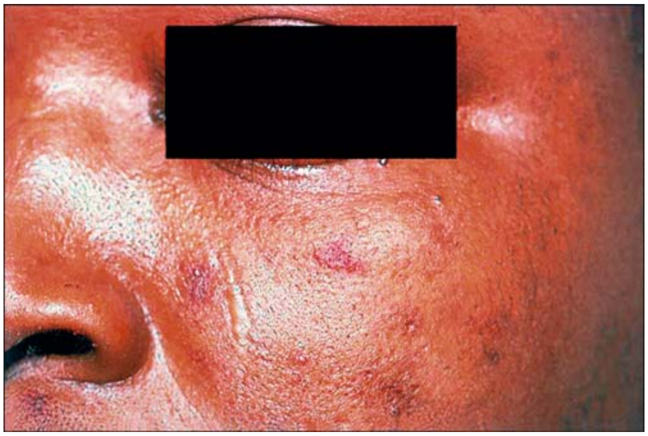

FIGURE 21-6 ■ Early cutaneous lesions of meningococcemia. (From Tyring S, Lupi O, Hengge U: Tropical Dermatology. Courtesy of Dr. Luc Van Kaer. Churchill Livingstone, New York, 2005, with permission.)

pneumoniae. There are now three quadrivalent vaccines against the causative organism *Neisseria meningitidis*, targeting serogroups A, C, W-135, and Y. There are also serogroup-independent vaccines that are effective against serogroup B but, currently, none is effective against serogroup X. Worldwide, meningococcal infections remain one of the leading causes of meningitis in children.

Lyme Borreliosis

The characteristic "target lesion" (*erythema chronicum migrans*) that spreads centrifugally from the site of a prolonged bite by a tick infected with the spirochete *Borrelia burgdorferi* is pathognomonic of early-stage Lyme disease. This cutaneous lesion first develops within a few days to weeks after the infecting bite by the tiny tick, *Ixodes dammini*. The characteristic cutaneous lesion is so named because of the fancied resemblance to a target. The erythematous circumference of the lesion advances over the course of days to weeks up to a diameter of 5 cm, leaving behind a trailing central area of clearing and a persistent erythematous papule at the very center, the site of the original tick bite (Fig. 21-7). This lesion develops in about 85 percent of infected individuals, facilitating clinical diagnosis for the subsequent syndrome of migratory arthralgias and later neurologic dysfunction. However, a high degree of clinical suspicion and the use of a serologic test are necessary for diagnosis in the substantial minority of patients that do not develop the characteristic target lesion.

Although neurologic signs can develop while the erythema migrans is still present, typically they do not appear until the cutaneous signs have resolved, after 6 to 12 months of migratory arthralgia that occasionally evolves into arthritis with an effusion in a large joint. The most common neurologic syndrome, affecting about 70 percent of untreated individuals, is a mild aseptic meningitis, with a mononeuritis multiplex or typical cranial nerve palsies. The latter include unilateral or bilateral facial palsies or lesions of the oculomotor, trigeminal, abducens, or eighth cranial nerve. Alternatively there may be a painful radiculopathy or plexitis. Other lesions reported less frequently include a myositis, patchy demyelination mimicking multiple sclerosis, or myelopathy with radiculopathies that could be mistaken for amyotrophic lateral sclerosis. Some untreated patients later develop an indolent diffuse encephalopathy. Further discussion is provided in Chapter 39.

Syphilis

As in Lyme borreliosis, dermatologic and neurologic manifestations are also temporally discordant in syphilis, which is related to infection with *Treponema pallidum*. The cutaneous manifestations are limited to the painless, indurated, rubbery genital chancre of primary syphilis in the days after infection, and the flat copper-colored lesions of the palms and soles, patchy alopecia, and mucous membrane patches seen in secondary syphilis, 2 to 4 months later (Figs. 21-8 and 21-9). Secondary syphilis is associated with a mild meningitis, sometimes with involvement of cranial nerves, typically the optic, facial, or acoustic.

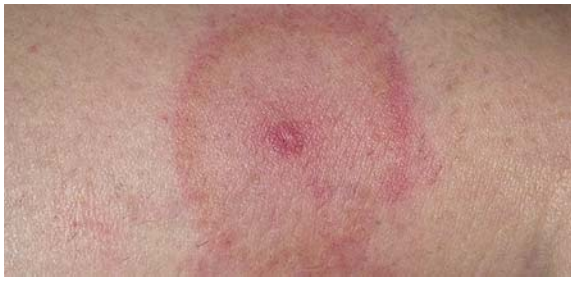

FIGURE 21-7 ■ Large 5-cm targetoid patch with central clearing, bright-red expanding border and central bite inflammation, characteristic of the erythema migrans rash of Lyme disease. (From Habif T, Campbell J, Chapman MS, et al: Dermatology DDX Deck. Saunders, Philadelphia, 2006, with permission.)

In contrast, cutaneous lesions will have resolved by the time of meningovascular syphilis, peaking 4 to 7 years after infection, and the neurologic manifestations of late-stage syphilis, namely the dementia (general paresis of the insane) and tabes dorsalis (Chapter 39). Thus the only exception to the temporal discordance of cutaneous and neurologic manifestations is their invariable association in secondary syphilis, in prenatal syphilis, and the rare occurrence of cutaneous nodules in late syphilis.

Fortunately, the late stages of syphilis have become quite rare. There had also been a period of diminishing prevalence of primary and secondary syphilis, but since 2000 there has been a steady increase of

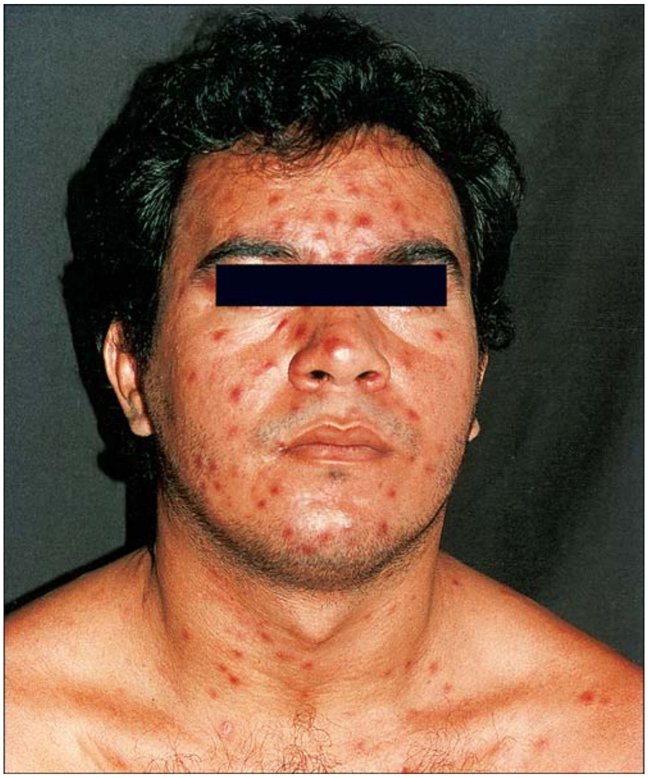

FIGURE 21-8 ■ Secondary syphilis: disseminated papular lesions. (From Tyring S, Lupi O, Hengge U: Tropical Dermatology. Courtesy of Dr. Luc Van Kaer. Churchill Livingstone, New York, 2005, with permission.)

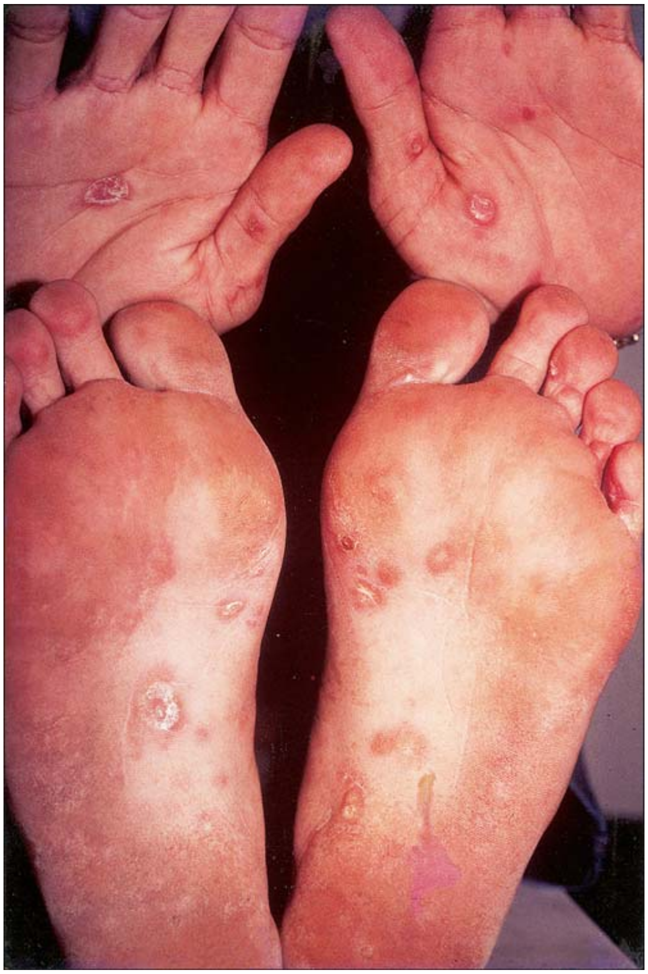

FIGURE 21-9 ■ Secondary syphilis: hyperkeratotic lesions on palms and soles. (From Tyring S, Lupi O, Hengge U: Tropical Dermatology. Courtesy of Dr. Luc Van Kaer. Churchill Livingstone, New York, 2005, with permission.)

incidence up to 16.9 per 100,000 in men and 2.3 per 100,000 in women, with a concomitant rise of congenital syphilis. Much of this increase has occurred in association with HIV-AIDS, which has also contributed to an altered natural history, including an occasional novel presentation that mimics that of herpes simplex encephalitis (but is responsive to treatment with penicillin), with focal lesions in the temporal lobe and status epilepticus or periodic lateralized discharges in the electroencephalogram.

Careful studies have also brought to light previously under-recognized syndromes of otologic syphilis, characterized by early sensorineural hearing loss and occasionally by vestibular dysfunction as well; and of ocular syphilis, mostly an early posterior uveitis affecting the choroid, retina, and pigmentary retinal epithelium. Involvement of the uveal tract also characterizes several other neurocutaneous disorders. Uveomeningitis is an occasional presentation of sarcoid, Behçet disease, and systemic lupus erythematosus, described in the following sections. It is also typical of the rare Vogt–Koyanagi–Harada syndrome, in which a prodromal meningoencephalitis precedes uveitis as well as the characteristic dermatologic findings of leukoderma with symmetric patches of vitiligo (involving the head, neck, shoulders, and eyelids), alopecia, and poliosis.

Sarcoidosis

Both the cutaneous and neurologic manifestations of sarcoidosis (discussed in Chapter 49) are notoriously variable, complicating early diagnosis.[9] Indeed, only 20 to 30 percent of patients with sarcoid have cutaneous lesions, and only 3 to 10 percent have neurologic manifestations. The most typical neurologic presentation is that of a mild aseptic meningitis, with or without cranial nerve palsies. Typically these are unilateral or bilateral facial nerve palsies, but optic, auditory or vestibular neuropathies may occur as well. A wide variety of other neurologic manifestations also occur (Chapter 49).

The cutaneous manifestations of sarcoid are more frequent but are also highly variable. There can be acute lesions such as erythema nodosum, vesicles, and maculopapular rash. These annular lesions, papules, or nodules are either skin-colored, violaceous, or brownish-red, often appearing on the face. Chronic lesions include lupus pernio (large, bluish red, dusty, violaceous infiltrated nodules and plaques, which generally appear on the cheeks, ears, fingers, and nose), plaque, scars, and keloids. The rare angiolupoid form of sarcoidosis consists of orange-red or reddish-brown soft, well-demarcated lesions.

Behçet Disease

This poorly understood inflammatory disease is characterized by a triad of recurrent oral and genital ulceration and uveitis, most commonly seen in populations along the old “Silk Road.” The majority of patients have additional cutaneous abnormalities including papillopustular lesions, erythema nodosum, and a pathergy reaction (pustulation at the site of trauma). The classic triad forms the basis of the current criteria for diagnosis, which is entirely clinical: recurrent oral ulceration (at least three times in a year) plus two of the following: (1) recurrent genital ulceration; (2) ocular lesions (uveitis, retinal vasculitis, or cells in the vitreous); and (3) skin lesions (erythema nodosum, pseudofolliculitis). Other common manifestations are arthritis, present in up to half of individuals; subcutaneous thrombophlebitis in about a quarter; and, in Japan, gastrointestinal lesions that affect about one-third. In contrast, neurologic complications affect only 10 percent or less of patients with Behçet disease, either as parenchymal or neurovascular disease. These two categories are not mutually exclusive; both parenchymal and neurovascular disease can affect a substantial minority of these patients. The pathology of the parenchymal disease is a "perivasculitis" rather than a vasculitis. There are infiltrates of polymorphonuclear leukocytes, eosinophils, lymphocytes, and macrophages without infiltration of blood vessel walls or necrosis of endothelial cells. The typical MRI picture of brainstem meningoencephalitis is that of a unilateral T2-enhancing lesion of the upper brainstem. Less frequent manifestations of parenchymal disease are seizures, transverse myelopathy, diffuse encephalopathy, or, much less commonly, an optic neuropathy. In some instances, the MRI appearance may resemble that of a glioma. Movement disorders and peripheral neuropathy are rare. Although venous occlusion is common, stroke resulting from arterial occlusions is rare, occurring in about 1 percent. Intracranial venous sinus thrombosis presents as increased intracranial pressure, a presentation that also sometimes occurs in the absence of radiographically demonstrable sinus or venous occlusion.

This disorder usually presents in young men, aged 20 to 40 years, but women are also affected, albeit less often. Most patients respond to treatment with corticosteroids, although about 20 percent are left with significant residual neurologic impairment and 10 percent succumb within a decade of diagnosis. Some practitioners supplement treatment of sinus thrombosis with anticoagulants after ruling out a pulmonary aneurysm, whereas others find corticosteroid treatment to be adequate. The course may be monophasic, relapsing remitting, or, most ominously, progressive.

INTERMITTENT ENCEPHALOPATHIES

Intermittent nonfocal impairment of the CNS culminating in psychiatric disturbance, confusion, delirium, stupor, or coma may result from trauma, infection, inflammation, and a wide variety of metabolic insults, some with cutaneous manifestations, as summarized in Table 21-3. Indeed, two of the most common—diabetic coma and intoxication with alcohol—are associated with cutaneous manifestations well known to most practicing physicians. The focus of this section is therefore on less common and perhaps less well-known neurocutaneous intermittent encephalopathies.

Systemic Lupus Erythematosus

Cutaneous abnormalities (malar, discoid, or photosensitive rash; Fig. 21-10) are present in at least 80 percent of these patients, with malar rash topping the list of the 17 classification criteria published by the Systemic Lupus International Collaborating Clinics, of which four are necessary for diagnosis. The others are features readily recognizable as immunologic abnormalities: serologic findings in the blood; arthritis; serositis of pleura or pericardium; glomerulonephritis or proteinuria; and hemolytic anemia, lymphopenia, or thrombocytopenia.[10] Rounding out the list are the nonspecific neurologic symptoms, including psychosis, which can be a presenting feature before the development of signs more typically associated with autoimmune disease. Because lupus typically presents between the ages of 15 and 25, which is also the peak age of onset of schizophrenia, a disorder considerably more prevalent than lupus, many patients are hospitalized in psychiatric wards before the true nature of their disease is recognized, often by appreciation of cutaneous abnormalities.

Although common, psychiatric signs and symptoms of a diffuse encephalopathy are but one of many less common but not infrequent manifestations of CNS lupus, others being seizures; aseptic meningitis; stroke (most commonly ischemic, either embolic from marantic endocarditis or mural cardiac thrombi after myocardial infarction, or from carotid atherosclerosis); chorea; relapsing-remitting disease resembling multiple sclerosis; and movement disorders. In addition, there is the more localized posterior reversible encephalopathy syndrome (PRES), a disorder with reversible subcortical vasogenic brain edema caused by endothelial dysfunction that presents with headaches, seizures, altered mental status, cortical blindness, vomiting, and focal deficits. Although occurring with other autoimmune disorders, this rare encephalopathy is encountered most commonly in association with systemic lupus. Systematic clinical trials have yet to be performed, but a favorable clinical response seems to follow control of blood pressure and seizures and elimination of

TABLE 21-3 ■ Intermittent Encephalopathy with Cutaneous Manifestations

Disorder	Cutaneous Lesions	Neurologic Features
Alcoholism	Telangiectasia	Intoxication, delirium tremens, neuropathy, Wernicke–Korsakoff syndrome, Marchiafava–Bignami syndrome
Coproporphyria (OMIM 121300)	Photosensitivity	Peripheral neuropathy, crises of abdominal pain and mental changes
Ethylmalonic encephalopathy (OMIM 602473)	Petechiae	Pyramidal and extrapyramidal signs, ataxia, seizures, hyperintense lesions in basal ganglia on MRI
Diabetes mellitus	Poorly healing skin ulcers, necrobiosis lipoidica diabeticorum	Diabetic ketoacidosis, nonketotic hyperglycemic coma, insulin-induced hypoglycemic coma, lacunar stroke, neuropathy, retinopathy
Hemolytic-uremic syndrome, 1–6 (OMIM 235400, 612922–612926)	Purpura	Coma, seizures, hemiparesis, visual disturbances
Holocarboxylase synthetase deficiency (OMIM 253270)	Skin rash	Irritability, lethargy, coma, seizures, hypotonia, developmental delay, hypertonia
Hydroxykynureninuria (OMIM 236800)	Light-sensitive rash	Intermittent, nonprogressive, ataxic encephalopathy
Letterer–Siwe disease (OMIM 246400)	Diffuse papulovesicular rash, scaly petechial dermatitis, intertriginous denudation, seborrhea, stomatitis	Encephalopathy
Methylmalonic aciduria and homocystinuria, CBLF type (OMIM 277380)	Reticulated pigmentation and rashes	Encephalopathy, hypotonia, lethargy, developmental delay, ataxia
Murine typhus	Macular rash	Headache, encephalopathy, and nuchal rigidity
Propionic acidemia (OMIM 606054)	Dermatitis acidemica	Acute encephalopathy, axial hypotonia, limb hypertonia, psychomotor retardation, cerebral atrophy, dystonia, cerebellar hemorrhage, ischemic stroke of basal ganglia
Shaken baby syndrome	Ecchymoses, purpura	Subdural hematomas, subarachnoid hemorrhage, parenchymal lacerations
Systemic lupus erythematosus	Photosensitivity, malar rash, telangiectasia, discoid lupus, patchy alopecia, mucosal ulcers, angioneurotic edema, Raynaud phenomenon, subcutaneous nodules, palpable purpura, gangrene, erythema multiforme	Encephalopathy, ischemic and hemorrhagic stroke, chorea, multifocal demyelination, peripheral neuropathies
Thrombotic thrombocytopenic purpura	Purpura	Rapidly evolving encephalopathy
Variegate porphyria (OMIM 176200)	Photosensitivity, blistering, skin fragility with chronic scarring of sun-exposed areas and postinflammatory hyperpigmentation	Crises with neuropsychiatric symptoms, abdominal pain, motor neuropathy

immunosuppressive drugs. The peripheral nervous system is also a frequent site of involvement with compressive neuropathies, most commonly carpal tunnel syndrome, affecting about 30 percent of patients, and a distal symmetric axonal neuropathy, sometimes with dysautonomia, about 20 percent. In about 1 percent or less, acute or chronic demyelinating neuropathies, mononeuritis multiplex, or cranial mononeuropathies occur.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) (Fig. 21-11) is a fulminant disorder that may be lethal if untreated.[11] Its clinical hallmark is rapid progression through confusion and obtundation to coma in the setting of thrombocytopenia resulting in cutaneous purpura, fever, Coombs-negative hemolytic anemia with fragmentation of erythrocytes, and renal

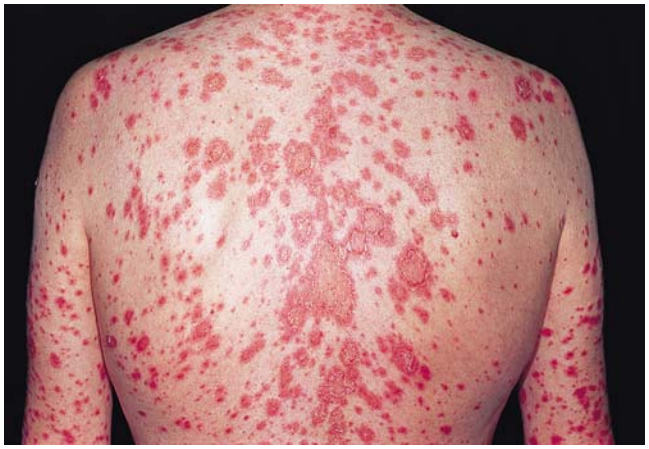

FIGURE 21-10 ■ Systemic lupus erythematosus. (From Callen J, Jorizzo J, Bolognia J, et al: Dermatological Signs of Internal Disease. Saunders, Philadelphia, 2009, with permission.)

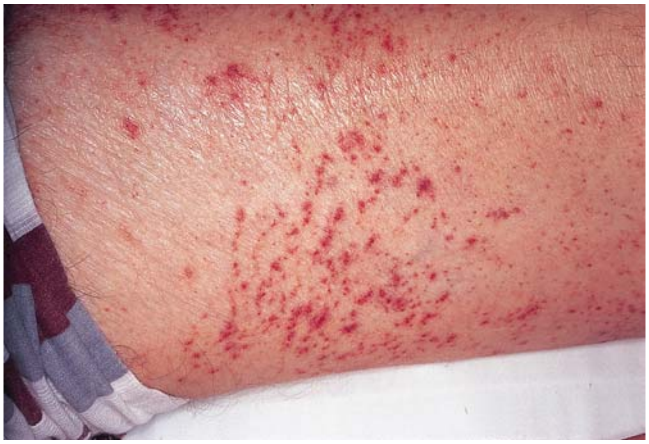

FIGURE 21-11 ■ Small petechiae in an individual with thrombocytopenia. (From Callen J, Jorizzo J, Bolognia J, et al: Dermatological Signs of Internal Disease. Saunders, Philadelphia, 2009, with permission.)

failure. Unlike lupus, this is not a vasculitis but a manifestation of pathologic aggregations of platelets. The adult-onset form is triggered by endothelial injury in various clinical settings: HIV-AIDS, pregnancy, metastatic cancer, or high-dose chemotherapy, or as a drug reaction. Most frequently there is an autoantibody-mediated depletion of an enzyme (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, or ADAMTS13, also known as von Willebrand factor-cleaving protease or VWFCP) that cleaves very high-molecular-weight complexes of von Willebrand factor, which can cause platelet adhesion and thrombosis. There is also a rare congenital familial TTP that is an autosomal recessive disorder (OMIM 274150) resulting from homozygosity for mutations of the ADAMTS13 gene encoded on chromosome 9q34.2. The congenital form, also known as Schulman–Upshaw syndrome, is associated with neonatal jaundice and a propensity to recurrences that require treatment with fresh frozen plasma.

Either form can be treated with plasmapheresis and exchange transfusion to remove the uncleaved high-molecular-weight complexes of von Willebrand factor and to replenish ADAMTS13. When needed, prophylaxis to prevent relapse of the acquired forms with autoantibodies to ADAMTS13 can also be obtained with corticosteroids, cyclosporine, or rituximab, an antibody directed at CD20, a cell-surface antigen of antibody-secreting B lymphocytes. Prompt recognition and treatment of this formerly lethal disorder results in recovery without residual neurologic or renal dysfunction, but mortality is still estimated at 10 to 20 percent.

The disorder must be distinguished from the similar hemolytic-uremic syndrome, of which there are several heritable susceptibility syndromes (OMIM 235400, 612922–612926). This disease occurs in children under age 3, usually after a prodromal diarrheal illness resulting from serotoxin-producing *Escherichia coli*, and is not always associated with encephalopathy. Six genes have been identified that confer susceptibility to this less-threatening disorder, all of them related to the complement system, a quite distinct mechanism from that underlying TTP.

Porphyria

The porphyrias are a family of genetically unrelated disorders resulting from mutations that disrupt heme metabolism. Clinically they can be divided into the hepatic porphyrias, which have neurologic but no cutaneous manifestations, and the cutaneous porphyrias, in which the opposite is true. Thus, none are neurocutaneous disorders, with the exception of variegate porphyria (OMIM 176200; heterozygous mutation of the protoporphyrinogen oxidase gene on chromosome 1q23.3, encoding the penultimate enzyme in the heme biosynthetic pathway) and coproporphyria (OMIM 121300; heterozygous mutation of the coproporphyrinogen oxidase gene on chromosome 3q11.2-q12.1). In both of these disorders, there is increased photosensitivity of the skin, and in variegate porphyria, fragility of the skin with blistering and chronic scarring of sun-exposed areas, followed by postinflammatory hyperpigmentation. In both, certain drugs induce a delirious encephalopathic crisis with psychotic symptoms, as well as neuropathic abdominal pain, constipation, and vomiting. In addition to the peripherally mediated abdominal crises there is a severe interictal peripheral neuropathy, which in variegate porphyria includes bulbar involvement as well as symmetric motor impairment in the extremities.

Both of these disorders violate the general rule of thumb that hereditary enzyme deficiencies are recessive disorders. In both, heterozygosity for a single mutant allele is sufficient to give rise to the disease phenotype, accounting for the unusual pattern of dominant inheritance for a metabolic disorder.

DEMENTIA

Certain neurocutaneous disorders lead to a progressive loss of cognitive ability. Two important examples are described in greater detail in the following paragraphs.

HIV-AIDS

Cognitive impairment, ranging in severity from mild HIV-1-associated neurocognitive disorder (HAND) to a severe progressive dementia, as well as a peripheral neuropathy, continue to be significant neurologic manifestations of HIV-AIDS, despite the availability of combination antiretroviral therapy.[12] The incidence of severe AIDS-related dementia has decreased, as have a number of adventitious infections of the nervous system in AIDS patients, including progressive multifocal encephalopathy, tuberculosis, toxoplasmosis, and infection with cytomegalovirus. However, the incidence of milder cognitive impairment persists, for reasons not yet understood. These and other neurologic aspects of HIV-AIDS are discussed in Chapter 43. Cutaneous manifestations have always been a hallmark of HIV-AIDS, affecting an estimated 85 percent of patients. A major clue in the early history of our understanding of AIDS was the high frequency of an unusual rapidly growing cutaneous tumor, atypical Kaposi sarcoma, in young homosexual men. Cutaneous herpes zoster or, more rarely, disseminated cryptococcal infection with cutaneous lesions resembling molluscum contagiosum may also be AIDS-defining events in HIV-positive individuals. The most common cutaneous manifestation, however, is seborrheic dermatitis, a chronic inflammation of the scalp and face, and, less commonly, intertriginous areas such as axillae and groin. Other cutaneous manifestations are virally mediated verruca vulgaris and molluscum contagiosum, recurrent staphylococcal infections, and tinea corporis.

Cockayne Syndrome

Cockayne syndrome (OMIM 216400) is an autosomal recessive disorder of “cachectic dwarfism” and significant cutaneous and neurologic abnormalities, with progressive dementia and multiple systemic abnormalities, that usually results in death in early adolescence, but with occasional survival to young adulthood. Other CNS abnormalities include microcephaly, calcifications of the basal ganglia, patchy subcortical demyelination, normal-pressure hydrocephalus, sensorineural hearing loss, pigmentary retinopathy, optic atrophy, ataxia, nystagmus, and peripheral neuropathy.

The syndrome is a consequence of homozygosity for mutations in a DNA-repairing enzyme, excision-repair cross-complementing, group 8 (ERCC8) on chromosome 5q12.1 (Cockayne syndrome A, OMIM 216400) or ERCC6 on chromosome 10q11.23 (Cockayne syndrome B, OMIM 133540). The resulting deficit confers increased sensitivity to ultraviolet irradiation, but not to x-irradiation. In a striking contrast with ataxia telangiectasia and xeroderma pigmentosa, other neurocutaneous disorders resulting from defects in DNA repair, there is no increased susceptibility to infections or malignancy.

SEIZURE DISORDERS

A great many neurocutaneous syndromes are associated with seizures. Three syndromes frequently included by some authors under a broadened definition of phakomatosis are discussed here in greater detail.

Sturge–Weber Syndrome

The characteristic feature of the Sturge–Weber syndrome (OMIM 185300) is the congenital port wine stain (Fig. 21-12), typically in the distribution of one of the branches of the trigeminal nerve. If

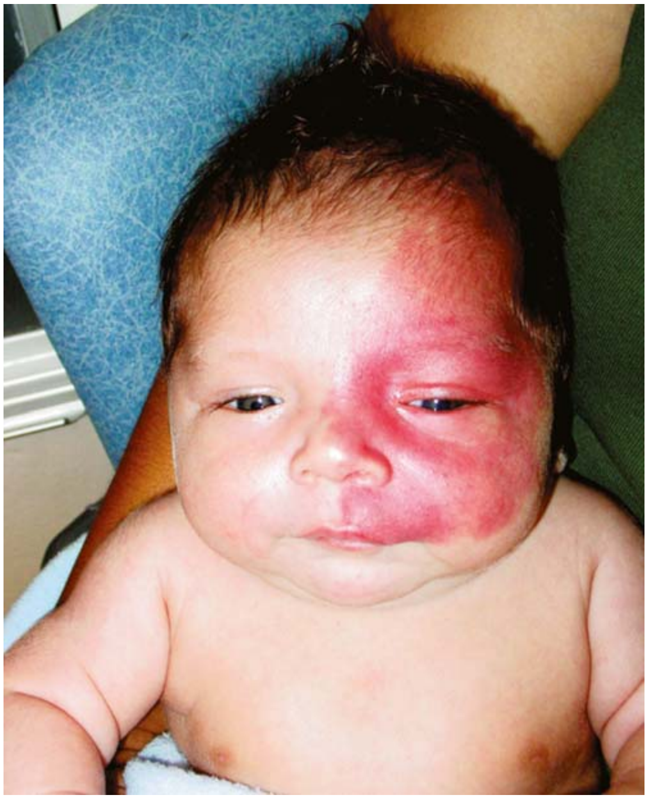

FIGURE 21-12 ■ Sturge–Weber syndrome: port-wine stain. (From Jones K: Smith's Recognizable Patterns of Human Malformation. Saunders, Philadelphia, 2005, with permission.)

this cutaneous lesion overlies the first division, there is a 75 percent chance that there will be a corresponding leptomeningeal venous malformation overlying focal deep cortical calcifications. This is often visible on skull radiographs as a "tram sign," the two tracks of which follow the contours of the calcified gyri.

Sturge–Weber syndrome is believed to result from somatic mosaicism for a mutation in the *GNAQ* gene (OMIM 600998) on chromosome 9q21-2, vertical transmission from parent to child never having been observed. The most common neurologic manifestation is epilepsy, typically partial complex seizures. The age of onset of seizures varies from birth to young adulthood. Often these seizures cannot be managed satisfactorily with anticonvulsants and therefore lead to consideration of surgery.

Unlike the classic phakomatoses with which it has occasionally been classified, Sturge–Weber syndrome is not associated with tumors of the nervous system or elsewhere. However, clinically significant neurologic involvement accompanies epilepsy in a significant proportion of affected individuals. Developmental delay and requirement for special education are typical of many patients with Sturge–Weber syndrome, but not for those who do not experience seizures. In contrast, the majority of individuals in both groups experience behavioral and emotional disturbances, as well as impediments to gainful employment, albeit to a greater degree in those with seizures. The major non-neurologic sequela is glaucoma, with onset as early as birth and as late as the fifth decade.

Incontinentia Pigmenti (Bloch–Sulzberger Disease)

Incontinentia pigmenti (OMIM 308300) is an X-linked dominant disorder that is lethal in utero to males, and is therefore only seen in those living female heterozygotes who preferentially inactivate the X chromosome bearing the mutant *NEMO* gene on Xp28 (a regulatory kinase of an inhibitor of the kappa light polypeptide gene enhancer in B cells) by lyonization. There is selective loss of cells expressing the X chromosome with the mutant gene at the time of birth, a process that continues until completion in young adulthood, at which time only cells expressing the normal X chromosome remain. This gradual elimination of cells expressing the mutant gene appears to be temporally correlated with the course of the characteristic cutaneous disorder, which occurs in four stages: (1) within hours to days of birth, lines of erythema develop into inflammatory vesicles that last from weeks to months; (2) these lesions then develop into verrucous, wart-like patches that persist for months; (3) hyperpigmentation develops, very gradually becoming pale and finally disappearing by age 20 years; and (4) dermal scarring develops in the final stage (Figs. 21-13 and 21-14). Hair loss may affect the scalp and other parts of the body, and there may be lined or pitted nails and toenails.

Seizures are the most common neurologic manifestation, occurring in about 70 percent of affected women, followed by various motor impairments (40%), cognitive impairment (30%), and microcephaly (7%). Structural abnormalities detectable by brain scanning include focal atrophy, infarcts, and lesions of the corpus callosum.

Classic Bloch–Sulzberger disease, as described above, had previously been called incontinentia pigmenti type II (IP2), IP1 being a term erroneously

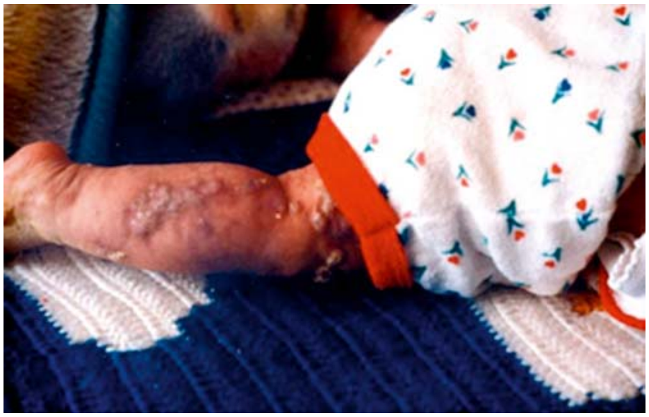

FIGURE 21-13 ■ Incontinentia pigmenti (Bloch–Sulzberger) stage 3: the beginning of hyperpigmentation. (From Kurlemann G: Neurocutaneous syndromes. Handb Clin Neurol 108:513, 2012, with permission.)

assigned by earlier investigators to some cases of hypomelanosis of Ito (OMIM 300337), which does not represent a distinct entity but is rather a manifestation of many different states of mosaicism. The hypopigmented skin lesions in hypomelanosis have been described as the "negative pattern" of the hyperpigmented lesions of incontinentia pigmenti. Neurologic abnormalities, typically seizures, are quite variable but can include severe mental retardation. The most prominent neuroanatomic abnormalities are histologically benign cortical heterotopias. It is best that the IP1/IP2 terminology be discarded, these disorders being both clinically and genetically distinct.

Linear Sebaceous Nevus Syndrome

Another dominant-lethal neurocutaneous syndrome associated with epilepsy that survives only by somatic mosaicism is the linear sebaceous nevus syndrome (OMIM 163200), also known as the Schimmelpenning–Feuerstein–Mims syndrome (Fig. 21-15). The characteristic sebaceous nevi typically present in the first year of life and persist through adulthood, and are often the site of secondary lesions such as basal cell carcinomas, hemangiomas, hypopigmentation, trichoblastoma, syringocystadenoma papilliferum, and central giant cell granuloma. Neurologic involvement (most commonly seizures, but also mental retardation, ophthalmoplegia, hemimegencephaly, attention deficit disorder) is only present in about 7 percent of individuals, who can present with any of a large variety of systemic abnormalities including coarctation of the aorta, horseshoe kidney, phosphaturia,

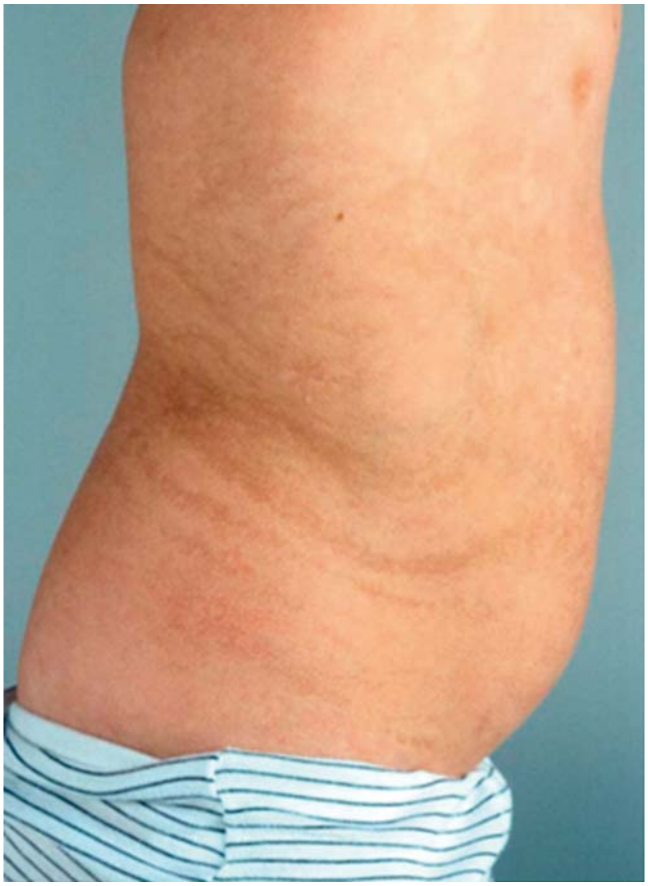

FIGURE 21-14 ■ Incontinentia pigmenti (Bloch–Sulzberger) stage 4: hypopigmentation on the trunk. (From Kurlemann G: Neurocutaneous syndromes. Handb Clin Neurol 108:513, 2012, with permission.)

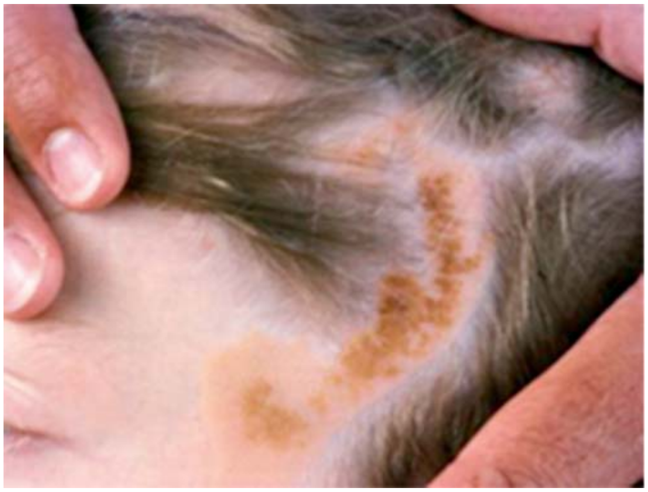

FIGURE 21-15 ■ Linear nevus sebaceous above the left eye near the hairline in Schimmelpenning–Feuerstein–Mims syndrome. (From Kurlemann G: Neurocutaneous syndromes. Handb Clin Neurol 108:513, 2012, with permission.)

osteopenia with fractures, and short stature. This disorder results from a mutation in either of two RAS genes: *KRAS* (V-Ki-Ras2 kirsten rat sarcoma viral oncogene homolog gene on chromosome 12p12.1) or *HRAS* (V-Ha-Ras Harvey rat sarcoma viral oncogene homolog gene on chromosome 11p15.5).

ATAXIA

Neurocutaneous disorders in which ataxia is a prominent feature are listed in Table 21-4. Four representative disorders are described in the following paragraphs.

TABLE 21-4 ■ Ataxia with Cutaneous Manifestations

Disorder	Cutaneous Lesions	Neurologic Features
Acrodermatitis enteropathica, zinc-deficiency type (OMIM 201100)	Bullous, pustular dermatitis of extremities; oral, anal, and genital areas dermatitis; impaired wound healing	Lethargy; ataxia; tremors; emotional lability
Angiomatosis, diffuse corticomeningeal, of Divry & van Bogaert (OMIM 206570)	Cutis marmorata; telangiectasia	Seizures; dementia; ataxia; dysarthria; pseudobulbar symptoms; emotional lability
Ataxia-telangiectasia (OMIM 208900)	Cutaneous telangiectasia; café-au-lait spots; progeric and sclerodermatous changes	Hyporeflexia; dysarthria; ataxia; choreoathetosis; seizures; oculomotor abnormalities
Biotinidase deficiency (OMIM 253260)	Seborrheic dermatitis; skin infections	Seizures; ataxia; developmental delay
Celiac disease; CD (OMIM 212750)	Dermatitis herpetiformis; follicular keratosis	Peripheral neuropathy; ataxia; anxiety; depression; cerebral calcification
Cerebrotendinous xanthomatosis (OMIM 213700)	Tuberous xanthoma; xanthelasma	Dementia; spasticity; ataxia; pseudobulbar palsy; psychiatric symptoms; leukoencephalopathy
Cowden disease (OMIM 158350)	Multiple facial papules; acral keratosis; palmoplantar keratosis; multiple skin tags; facial trichilemmomas; subcutaneous lipomas	Mild to moderate mental retardation; Lhermitte—Duclos disease; appendicular ataxia; cerebellar gangliocytoma; meningioma
Dyskeratosis congenita, autosomal dominant, 3 (OMIM 613990)	Reticular pigmentation pattern; leukoplakia; dry skin	Speech delay; learning difficulties; intracranial calcifications; ataxia; cerebellar hypoplasia
Flynn—Aird disease (OMIM 136300)	Skin atrophy, chronic ulceration	Seizures; dementia; ataxia; peripheral neuropathy
Hartnup disorder (OMIM 234500)	Photosensitive dermatitis	Intermittent ataxia; seizures; hypertonia; hyperreflexia; emotional instability; psychosis
Hemophagocytic lymphohistiocytosis (OMIM 267700, 603553)	Purpuric rashes	Seizures; meningitis; encephalitis; ataxia; coma; increased intracranial pressure; delayed psychomotor development
Hydroxykynureninuria (OMIM 236800)	Light-sensitive rash	Intermittent nonprogressive ataxic encephalopathy
Neuroblastoma (OMIM 256700)	Bluish skin nodules	Paraneoplastic opsoclonus, myoclonus, and/or ataxia; spinal cord compression
PHACE association (OMIM 606519)	Hemangioma, facial, plaque-like	Developmental delay; Dandy—Walker malformation; seizures; migraine headaches (ipsilateral to facial hemangioma); cerebral infarction
Plasminogen deficiency, type I (OMIM 217090)	Juvenile colloid milium; small papules on sun-exposed areas	Dandy—Walker malformation; macrocephaly; adult onset of symptoms has been reported
Refsum disease (OMIM 266500)	Ichthyosis	Ataxia; peripheral neuropathy; retinitis pigmentosa; sensorineural deafness; anosmia
Renal tubulopathy, diabetes mellitus, and cerebellar ataxia (OMIM 560000)	Mottled pigmentation of photoexposed areas; episodic cold-triggered erythrocyanosis of toes and fingers	Myoclonic jerks; ataxia; hypotonia; psychomotor regression
Revesz syndrome (OMIM 268130)	Fine, reticulate skin pigmentation (trunk, palm, and soles)	Psychomotor retardation; cerebellar hypoplasia; ataxia; cerebral calcifications; hypertonia; progressive neurologic deterioration
Spinocerebellar ataxia 34 (OMIM 133190)	Erythrokeratodermia; papulosquamous erythematous plaques; hyperkeratosis	Spinocerebellar ataxia; mild spasticity; dysarthria

Ataxia Telangiectasia

Also known as Louis–Bar syndrome (OMIM 208900), the cardinal features of this autosomal recessive disorder are cerebellar ataxia, cutaneous telangiectases, immune defects, and a predisposition to malignancy (Fig. 21-16). The invariable, progressive neurologic disorder, chiefly ataxia, begins at birth, often initially causing diagnostic confusion because the characteristic oculocutaneous telangiectasias do not appear until 3 to 5 years of age. The ataxia is initially truncal and only later appendicular. It is associated with a characteristic oculomotor apraxia. A large-fiber neuropathy becomes evident in late childhood and spinal muscular atrophy evolves in early adulthood. About 10 percent of individuals also develop a more complex movement disorder, with choreoathetosis that can be severe.

Major issues in clinical management include a strong predisposition to malignancy (chiefly leukemia and lymphoma, but also others), as well as impairment of both humoral and cellular immunity, often manifested by frequent sinopulmonary infections. A marked hypersensitivity to ionizing radiation is a fundamental feature of this disorder: the need to minimize exposure requires significant modification of radiotherapeutic dosages and the use of radiologic monitoring.

Affected individuals are homozygous for mutation of the ataxia-telangiectasia mutated (*ATM*) gene, consisting of 66 exons encoding a phosphatidylinositol 3-kinase that repairs certain types of DNA damage, on chromosome 11q22.3. As such, it fits the classic definition of an autosomal recessive disorder. However, heterozygotes for *ATM* mutations, who cannot be identified by routine clinical examination and who vastly outnumber manifesting homozygotes, have a significantly increased sensitivity to radiation as well as increased propensity to certain types of malignancy. As such, they represent a larger concern to public health than do the rare, unfortunate homozygotes.

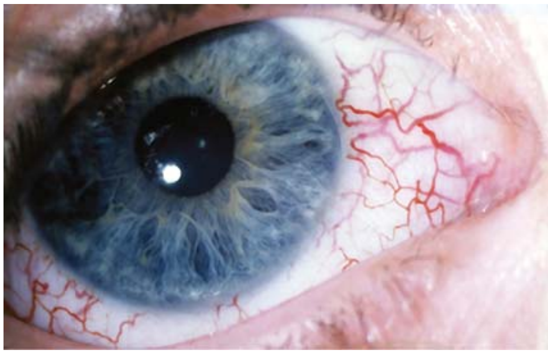

FIGURE 21-16 ■ Ataxia-telangiectasia: bulbar conjunctiva. (From Jones K: Smith's Recognizable Patterns of Human Malformation. Saunders, Philadelphia, 2005, with permission.)

Cerebrotendinous Xanthomatosis

The dermatologic manifestations of this lipid storage disorder (OMIM 213700) are tuberous xanthomata and xanthelasma, similar to the characteristic deposits of cholesterol and cholestanol in multiple other tissues, particularly in the Achilles tendon, for which deposits the disorder is named. The progressive neurologic disorder begins in puberty with ataxia and progresses to involve the spinal cord and brainstem. These cardinal features correlate with focal lipid deposits, visible on either CT or MRI scans, in the cerebellar white matter and the cerebral peduncles as well as the brainstem and basal ganglia. Unlike in ataxia telangiectasia, a progressive dementia may develop as well as psychotic symptoms such as delusions and hallucinations. Systemic symptoms include cataracts, respiratory complaints, bony fragility, and myocardial infarction, even though plasma cholesterol levels are either normal or only modestly elevated.

This autosomal recessive disorder results from the lack of functional sterol 27-hydroxylase, an enzyme involved in the synthesis of bile acids, resulting from mutations in the *CYP27A1* gene on chromosome 2q35. This metabolic abnormality leads to decreased synthesis of bile acids and a compensatory increase in the activity of the rate-limiting enzyme in bile acid synthesis, cholesterol 7α-hydroxylase, and accumulation of 7α-hydroxylated bile acid precursors, including a precursor to cholestanol that readily crosses the blood–brain barrier. This complex biochemistry can be ameliorated by treatment with cholic acid, chenodeoxycholic acid, and statins, which reduce xanthomata and improve central neurologic symptoms, but not the axonal peripheral neuropathy which is part of this systemic disorder.

Classic Refsum Disease

This is a complex neurocutaneous disorder in which progressive ataxia is part of an invariable tetrad that also includes peripheral neuropathy, retinitis pigmentosa, and elevated protein in acellular cerebrospinal fluid (OMIM 266500). In most cases, there is also progressive hearing loss. The classic dermatologic abnormality of ichthyosis is less common, as are cardiac abnormalities and a skeletal abnormality, multiple epiphyseal dysplasia. Classic Refsum disease is to be distinguished from the genetically and clinically distinct infantile Refsum disease, which is one of a heterogeneous group of peroxisomal biogenesis disorders that include Zellweger syndrome and neonatal adrenoleukodystrophy.

Classic Refsum disease is a treatable autosomal recessive disorder. Affected individuals are homozygous for inactivating mutations in the gene encoding phytanoyl-CoA hydroxylase on chromosome 10p13. As a result, there is impaired degradation of phytanic acid, an unusual branched-chain fatty acid derived exclusively from dietary sources. Restriction of foods containing chlorophyll and phytols leads to reduction of blood levels of phytanic acid and some amelioration of clinical signs. Plasmapheresis may allow modest liberalization of the diet.

Hartnup Disease and Related Disorders

Unlike the previously described neurocutaneous ataxias, which are progressive when treatment is unavailable, Hartnup disease (OMIM 234500) is an intermittent ataxia, associated with a light-sensitive, pellagra-like skin rash and emotional instability. The characteristic rash is symmetric, hyperkeratotic, hyperpigmented, and desquamated in exposed areas.

It results from homozygosity for mutations that alter the activity of system B(0) neutral amino acid transporter 1, also referred to as solute carrier family 6 (neurotransmitter transporter), member 19 (SLC6A19), an amino acid transporter present in the intestinal brush border and renal cortical proximal tubules, but not in the skin or the nervous system. For this reason, signs and symptoms can be attributed to low plasma levels of neutral amino acids, principally tryptophan and methionine, resulting from aminoaciduria and selective intestinal malabsorption. The frequency of Hartnup disease is similar to that of phenylketonuria, that is, 1 in about 14,000 live births. Unlike phenylketonuria, however, Hartnup disease has no ill effects on the fetus because placental transport of amino acids is not affected. Indeed, despite this significant frequency, the full-blown classic disorder is now rarely seen in the United States because most diets supply sufficient levels of neutral amino acids to at least partially compensate for intestinal and renal losses.

A similar rash occurs in two other neurocutaneous disorders in which tryptophan metabolism is implicated. *Pellagra*, rarely seen in the developed world, results from dietary deficiency of a B vitamin, niacin, which can be taken directly in the diet or synthesized from dietary tryptophan, both of which are in short supply in a corn-based diet. This chronic wasting disease is characterized by a triad of dermatitis, dementia, and diarrhea.

Hydroxykynureninuria (OMIM 236800) is an autosomal recessive disorder resulting from deficiency of kynureninase, an enzyme apparently required for the synthesis of niacin from tryptophan. Its neurologic phenotype is intermediate between that of pellagra and Hartnup disease. In addition to the characteristic light-sensitive rash, there is a nonprogressive ataxic encephalopathy that can reversibly worsen under the stress of a viral infection, on occasion leading to coma and death.

MYELOPATHY

Transverse or compressive myelopathies may be rare presentations of a number of neurocutaneous syndromes. Two, in which myelopathy is a common presentation, are described here.

Rheumatoid Arthritis

Subcutaneous nodules at sites of trauma, such as extensor surfaces of forearms, posterior scalp, and ears are characteristic manifestations of rheumatoid arthritis. In addition, there may be painful papules of the finger pulp, bright red "liver palms," or a vivid washable yellow discoloration of the skin from inspissated sweat.

The most feared neurologic abnormality in rheumatoid arthritis is not from intrinsic inflammation of the nervous system but a potentially life-threatening compressive high cervical myelopathy resulting from localized pachymeningitis or arthritis with laxity of the atlantoaxial joint, present in about half of individuals with advanced rheumatoid arthritis. This can cause either horizontal atlantoaxial instability or vertical translation of the dens with a normal atlantoaxial interval. Repeated microtrauma to the craniocervical junction may give rise to a gradually progressive, high cervical myelopathy. However, moderately severe trauma from a fall or an otherwise minor motor vehicle accident can result in catastrophic, lethal, spinal cord compression.[13]

The high frequency of these potentially preventable complications requires screening with lateral radiographs of the cervical spine in the neutral position and in flexion to assess the atlantoaxial interval even in neurologically asymptomatic individuals in order to assess the potential for catastrophic subluxation. MRI of the craniocervical junction is useful for two purposes: (1) detection of an altered intraparenchymal signal indicating injury from milder repetitive compression due to minor subluxation of the atlantoaxial joint; and (2) for detection of an inflammatory pannus around the dens, which can further compromise the subarachnoid space. Neurosurgical intervention is warranted if there is a high degree of instability or evidence of myelopathy. Anatomy dictates the required intervention: a high degree of positional instability requires fusion; obliteration of the subarachnoid space without significant instability requires decompression.

Other neurologic complications of rheumatoid arthritis are discussed in detail in Chapter 50.

Sjögren Syndrome

Sjögren syndrome is characterized by autoimmune involvement of lacrimal and salivary glands, causing dry eyes and dry mouth (the sicca syndrome), but also by more widespread systemic and neurologic manifestations.[14] Cutaneous involvement, when present, is palpable purpura, a classic sign of cutaneous vasculitis. Both the central and the peripheral nervous systems are frequently also affected, as discussed in Chapter 50. The classic peripheral neurologic manifestation is a ganglionitis or a distal small-fiber axonal sensory neuropathy, but there may be multiple cranial neuropathies and mononeuritis multiplex as well. Although less frequent, the most common CNS presentation is a focal, transverse myelopathy with a T2 bright MRI lesion that spans several segments. This may mistakenly be attributed to multiple sclerosis, as may various other presentations of Sjögren syndrome including focal cerebral or brainstem lesions associated with perivenular inflammation, more often in the white matter than gray. Recognition of the sicca syndrome and cutaneous manifestations may therefore be critical in suggesting the correct diagnosis.

PERIPHERAL NEUROPATHY

Various entrapment neuropathies, mononeuropathies, plexopathies, distal symmetric, and cranial neuropathies with cutaneous manifestations are listed in Table 21-5. Three disorders in which peripheral nerve involvement is either the principal or only neurologic manifestation are described in this section.

Leprosy

Leprosy is also known as Hansen disease in honor of the Norwegian physician who discovered the causative organism, *Mycobacterium leprae*, in 1873. The disorder is discussed in detail in Chapter 41. Until the 1980s leprosy was perhaps the most common peripheral neuropathy and neurocutaneous disorder worldwide, affecting in excess of 10 million individuals and permanently disfiguring millions. A steady decline in its incidence has followed the introduction of multidrug therapy. The majority of cases are in the tropics, with about 50 percent of the cases in India, and high numbers in a periequatorial belt that includes Brazil, Madagascar, and Myanmar. About 250,000 new cases are diagnosed annually. Armadillos, the only other species to harbor the obligate intracellular bacillus, *M. leprae*, are still hunted for food in the American Southwest and can be a source of exposure to this infectious agent.

The neuropathy typically presents with characteristic skin lesions and a hypesthetic mononeuritis multiplex with palpably thickened nerves. The distribution of the mononeuritis is influenced by the organism's proclivity for endoneural invasion in the cool exposed face and extremities, as discussed in detail in Chapter 41. In addition to commonly affected superficial cutaneous nerves, there is frequent motor involvement in the distribution of the ulnar nerve and sensory involvement of the posterior tibial nerve.

Although all lepromatous neuropathy is a consequence of local mycobacterial invasion, the cutaneous manifestations depend on the strength of the host's immune response. A vigorous response leads to tuberculoid, or paucibacillary leprosy with

TABLE 21-5 ■ Peripheral Neuropathy with Cutaneous Manifestations

Disorder	Cutaneous Manifestations
AIDS	Seborrheic dermatitis, verruca vulgaris, molluscum contagiosum, Kaposi sarcoma
Alcoholism	Telangiectasias, malar rash, psoriasis and discoid eczema, exacerbation of rosacea, porphyria cutanea tarda, acne
Amyloidosis (primary)	Purpura in skin folds or flat surfaces or eyelids, papules, sometimes alopecia, rarely bullae on skin or oral mucosa
Angioedema, hereditary, type I (OMIM 106100)	Erythema marginatum
Arsenic poisoning	Dry scaly desquamation, linear hyperpigmentation of nails, Mees lines
Brachydactyly mental retardation syndrome (OMIM 600430)	Eczema
Cardiofaciocutaneous syndrome (OMIM 115150)	Severe atopic dermatitis, ichthyosis, hyperkeratosis (especially extensor surfaces), cavernous hemangiomas, keratosis pilaris, multiple palmar creases, multiple lentigines
Celiac disease (OMIM 212750)	Dermatitis herpetiformis, follicular keratosis
Cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma syndrome (OMIM 609528)	Palmoplantar keratoderma, ichthyosis
Cerebrotendinous xanthomatosis (OMIM 213700)	Tuberous xanthoma, xanthelasma
Chediak–Higashi (OMIM 214500)	Partial albinism, silvery blond hair
Coenzyme Q10 deficiency, primary, 2 (OMIM 614651)	Hypopigmentation, malar flush, livedo reticularis
Coproporphyria, hereditary (OMIM 121300)	Photosensitivity
Cronkhite–Canada gastrointestinal hamartomatous polyposis (OMIM 175500)	Alopecia, skin hyperpigmentation, onychodystrophy
Diabetes mellitus	Necrobiosis lipoidica diabeticorum, poorly healing ulcers
Diphtheria (cutaneous)	Jungle sore
Fabry disease (OMIM 610651)	Angiokeratoma
Flynn–Aird disease (OMIM 136300)	Skin atrophy, hyperkeratosis, chronic ulceration
Fucosidosis (OMIM 230000)	Angiokeratoma; thin, dry skin; anhidrosis
Hemochromatosis (OMIM 235200)	Bronze pigmentation, telangiectasias
Histiocytic reticulosis	Purpura, jaundice, erythroderma
Hyperoxaluria, primary, type I (OMIM 259900)	Livedo reticularis, calcinosis cutis metastatica, acrocyanosis
Impaired long-chain fatty acid oxidation	Congenital ichthyosis, ichthyosiform erythroderma
Kanzaki disease (OMIM 609242)	Angiokeratoma corporis diffusum, hyperkeratosis, dry skin, diffuse maculopapular eruption, telangiectasia on lips and oral mucosa
Leprosy	Hypopigmentation and hyperpigmentation, leonine facies, erythema nodosum leprosum, Lucio phenomenon
Linear sebaceous nevi of Jadassohn (OMIM 163200, Schimmelpenning–Feuerstein–Mims syndrome)	Sebaceous and epithelial nevi, linear nevus sebaceous
Lyme disease	Target lesions
Neurocutaneous melanosis (OMIM 249400)	Large multiple pigmented skin nevi ($>$20 cm), no malignant melanoma other than CNS
Pellagra	Erythematous photosensitive rash, erythema, vesicles, glossitis, malar and supraorbital hyperpigmentation, rhagades

(Continued)

TABLE 21-5 ■ (Continued)

Disorder	Cutaneous Manifestations
Peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease (OMIM 609136)	Hypopigmented skin patches
Phenylketonuria (OMIM 261600)	Pale pigmentation, dry skin, eczema, scleroderma
POEMS syndrome	Hyperpigmentation, thickening, verrucous angiomas, hirsutism, Raynaud phenomenon
Poikiloderma–spastic paraplegia	Poikiloderma: delicate, smooth, wasted skin
Refsum disease (classic) (OMIM 266500)	Ichthyosis
Sarcoidosis	Hypohidrosis, cicatricial alopecia; *acute*: erythema nodosum, vesicles, maculopapular rash; *chronic*: lupus pernio, plaques, scars, keloids
Sjögren syndrome	Purpura, Raynaud phenomenon, xerostomia, candidiasis
Spastic paraplegia 23 (OMIM 270750)	Patchy vitiligo, hyperpigmentation of exposed areas, lentigines
Stiff skin syndrome (OMIM 184900)	Thick, indurated skin over entire body
Systemic lupus erythematosus	Photosensitivity, malar rash, discoid lupus
Thallium intoxication	Hair loss
Trichorrhexis nodosa	Ichthyosis, flexural eczema, photosensitivity, short wooly hair
Vitamin B_{12} deficiency	Black nail pigmentation (nail bed and matrix), oral aphthae
Werner syndrome (pangeria) (OMIM 277700)	Scleroderma-like skin, graying hair and baldness, leg ulcers, progressive scalp alopecia, sparse body hair, telangiectasia, mottled pigmentation; loss of subcutaneous fat, subcutaneous calcification
Xeroderma pigmentosum (OMIM 610651)	Photosensitivity, early-onset skin cancer, atrophy, telangiectasia, actinic keratosis, angioma, keratoacanthomas

granuloma formation, anesthetic patches of skin adjacent to thickened peripheral nerves, and severe destruction of nerve. At the other end of the spectrum is lepromatous leprosy with widespread nodular cutaneous lesions (e.g., leonine facies) (Fig. 21-17) containing large quantities of *M. leprae*, leading to a more insidious destruction of nerves, in which there is an absence of a cell-mediated immune response. Most patients lie along a spectrum between these two extremes, depending in part on their complement of susceptibility genes, which have been mapped to a half-dozen gene loci, three of which have been associated with an identified gene (OMIM 610988, 613223, 248300).

Although the fully developed neurocutaneous syndrome is easily diagnosed in endemic areas even by individuals who are not medically trained, the long incubation period provides ample opportunity for transmission before the disease is evident. Furthermore, clinically evident nerve damage and disfigurement are irreversible. The recent development of antibody-based tests had given hope that presymptomatic leprosy could be diagnosed and treated, possibly as a final step to the goal of the World Health Organization of complete eradication of this neurocutaneous disorder. However, current versions of these tests still require improvement.

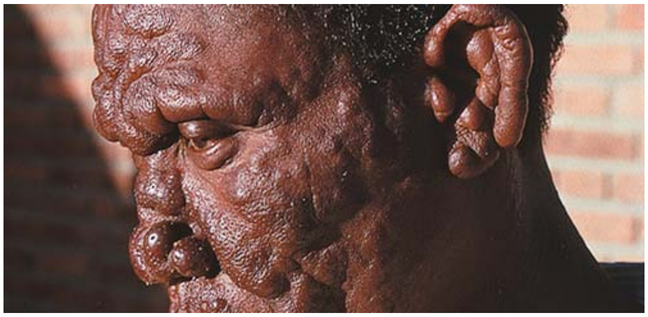

FIGURE 21-17 ■ Infiltrated nodules of the forehead and face resulting in the leonine facies of lepromatous leprosy. (From Peters W, Pasvol G: Atlas of Tropical Medicine and Parasitology. 6th Ed. Mosby, St Louis, 2007, with permission.)

Systemic Sclerosis

This disorder is often commonly referred to as scleroderma, which is the name more properly applied to its characteristic cutaneous manifestation—a thickening of the skin—that can also occur as an isolated syndrome independent of the systemic and neurologic manifestations of systemic sclerosis. Another cutaneous feature of systemic sclerosis is a diffuse hyperpigmentation. Various peripheral neuropathies are by far the most common manifestations of systemic sclerosis, the most common being carpal tunnel syndrome, which occurs in about a quarter of patients, and cranial neuropathies, especially trigeminal neuralgia. Less commonly there are symmetric axonal neuropathies, often with autonomic involvement, as well as mononeuritis multiplex and plexopathies. In contrast to the frequent involvement of the peripheral nerves, the links between systemic sclerosis and pathology of the CNS are much more tenuous, apart from asymptomatic calcification of the basal ganglia, which occurs in about one-third of affected individuals.

Systemic Vasculitis

The classic neurocutaneous presentation of palpable purpura and mononeuritis multiplex occurs in several types of systemic vasculitis, a heterogeneous and partially overlapping group of neurocutaneous disorders that include classic polyarteritis nodosa, Churg–Strauss allergic angiitis and granulomatosis, and Wegener granulomatosis. All three of these disorders affect small and medium-sized arteries, the first two as prime examples of a larger class of systemic necrotizing vasculitis. Occlusion of small arteries results in mononeuritis, an abrupt, painful ischemic infarction of the segment of a peripheral nerve in which perfusion is compromised. These three disorders differ histopathologically and clinically. They are discussed in detail in Chapter 50. In order of frequency, classic polyarteritis nodosa affects kidneys, joints, peripheral nervous system, skin, gastrointestinal tract, and the CNS, but never the lungs. During the course of the disease, peripheral nerve involvement is seen in over half of cases, though rarely as one of the presenting signs. In less than a quarter of cases, the necrotizing vasculitis of polyarteritis nodosa extends into the CNS.

In contrast, the lungs are affected in Churg–Strauss syndrome, a granulomatous disorder closely associated with asthma, and in Wegener granulomatosis, a distinct disorder of granulomatous vasculitis of the upper and lower respiratory tract. In Wegener granulomatosis, renal involvement dominates the clinical picture in about 75 percent of patients, cutaneous manifestations occur in about 50 percent, and neurologic manifestations in about 25 percent. Palpable purpura, the signature lesion of cutaneous vasculitis (Fig. 21-18), may be prominent, as may vesicles, papules, ulcers, and subcutaneous nodules. Nervous system involvement is usually peripheral, with a mononeuritis multiplex similar to that of polyarteritis nodosa being a frequent feature, but with a much lower frequency of CNS vasculitis.

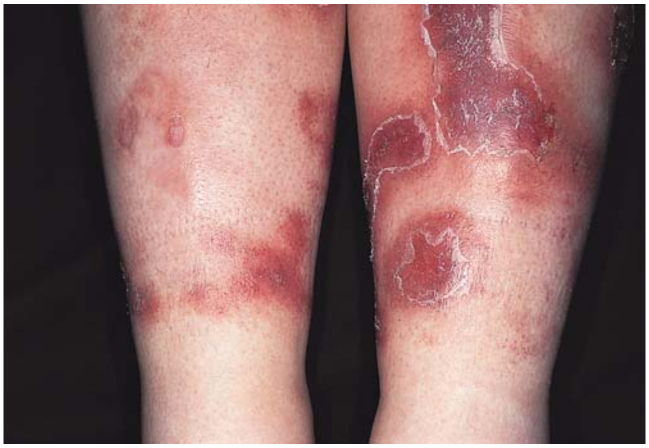

FIGURE 21-18 ■ Cutaneous small-vessel vasculitis was the first evidence of recurrence in this patient with Wegener granulomatosis. (From Callen J, Jorizzo J, Bolognia J, et al: Dermatological Signs of Internal Disease. Saunders, Philadelphia, 2009, with permission.)

Untreated, all three disorders are lethal. Treatment is based on corticosteroids and cyclophosphamide, except in the 20 percent of cases of polyarteritis nodosa with demonstrable blood levels of hepatitis B surface antigen, thought to be the inciting antigen for the pathophysiologic cascade initiated by deposition of immune complexes in the walls of blood vessels that attract the necrotizing leukocytic infiltrate. In such cases, there may be response to treatment with interferon-α and plasma exchange.

Different patterns of cutaneous and neurologic manifestations—sometimes including mononeuritis multiplex as a minor feature—occur in other disorders classified as vasculitis: notably Behçet disease and the vasculitis associated with certain connective tissue disorders, most notably systemic lupus erythematosus. Other vasculitic disorders, such as giant cell arteritis, with no cutaneous manifestations, or the primary cutaneous vasculitides, which by

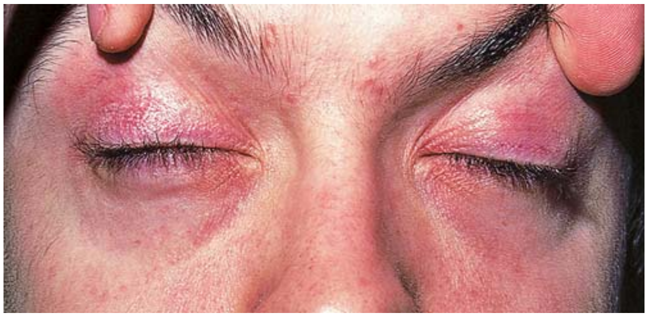

FIGURE 21-19 ■ Characteristic heliotrope rash of dermatomyositis on the eyelids. (From Habif T, Campbell J, Chapman MS, et al: Dermatology DDX Deck. Saunders, Philadelphia, 2006, with permission.)

definition have no neurologic or systemic manifestations, are not neurocutaneous syndromes and are not discussed here.

MYOPATHY

Dermatomyositis

Dermatomyositis is not "polymyositis with a rash" but a distinct vasculitis that can be diagnosed unequivocally by considering either the cutaneous or muscle pathology on its own.[15] Unlike polymyositis, it commonly affects children as well as adults. Photosensitivity either precedes or accompanies muscle weakness, facilitating diagnosis. This manifests as an erythematous rash over sun-exposed areas: the malar region, the "shawl" of the neck and shoulders, and the exposed anterior "V" of the chest as well as over the knuckles, malleoli, or other joints. Typically there is a distinctive heliotrope rash of the eyelids (Fig. 21-19). In about two-thirds of childhood cases, there is also subcutaneous calcification. These skin lesions may be the only clinically evident manifestation, especially when the muscle involvement is unusually mild. More typically, proximal limb-girdle weakness develops subacutely over weeks to months, often involving pharyngeal muscles and neck extensors, but with sparing of facial and extraocular muscles. The muscles may be tender. Muscle histology demonstrates a microangiopathy.

Dermatomyositis is associated with malignancy in about 15 percent of cases, more often in adults than in children. This is most often in the ovary, breast, or colon or a melanoma, but occasionally the lung or some other site is involved. Alternatively, it is occasionally seen in association with systemic sclerosis, with a rare Mendelian disorder (Barraquer–Simons syndrome, OMIM 608709) or as an isolated neurocutaneous syndrome.

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SECTION

6

Bone and Joint Disease

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CHAPTER

22

Neurologic Disorders Associated With Bone and Joint Disease

ANN NOELLE PONCELET ■ ANDREW P. ROSE-INNES

DEGENERATIVE DISEASE OF THE SPINE
  Cervical Spondylosis and Disc Disease
  Lumbar Disc Disease
LUMBAR SPINAL STENOSIS AND NEUROGENIC CLAUDICATION
OSTEOPOROSIS
OSTEOMALACIA
OSTEOPETROSIS
PAGET DISEASE OF BONE
  Inclusion-Body Myopathy, Paget Disease, and Frontotemporal Dementia
VERTEBRAL OSTEOMYELITIS
  Tuberculous Osteomyelitis
ANKYLOSING SPONDYLITIS
  Diffuse Idiopathic Skeletal Hyperostosis
RELAPSING POLYCHONDRITIS

The brain, spinal cord, cranial nerves, and spinal roots share an intimate anatomic relationship to the spine and skull; as a result, disorders of the skeletal system may result in neurologic compromise. This broad group of conditions includes congenital malformations as well as degenerative, metabolic, traumatic, neoplastic, infectious, and inflammatory disorders of the bones and joints. The craniosynostoses (premature closure of the cranial sutures) are covered in major texts of pediatric neurology and are not addressed here. The neurologic complications of trauma and neoplastic involvement of bone are covered in other chapters. The neurologic complications of rheumatoid arthritis and some additional connective tissue disorders are discussed separately in Chapter 50.

DEGENERATIVE DISEASE OF THE SPINE

Degenerative disease of the spine includes changes to both the intervertebral discs and the vertebrae ("spondylosis") that in general become more common with age. The lifelong mechanical stress sustained by the highly mobile cervical spine and the somewhat less mobile, weight-bearing lumbar spine accounts for the preponderance of degeneration in these two regions. Spinal degeneration may be entirely asymptomatic or may cause local or referred pain, radiculopathy, or myelopathy. Degenerative spinal disease is commonly found on imaging of asymptomatic older adults.[1]

The intervertebral discs change in composition and structure with age. From the second decade onward, disc degeneration and its consequent clinical manifestations become more frequent. Concomitant degeneration of the bony elements of the spine also occurs, including "lipping" of the superior and inferior margins of the vertebral bodies, the formation of osteophytes, osteoarthritic changes of the facet joints (subluxation, osteophytosis, and cartilaginous changes), narrowing of the intervertebral disc spaces, hypertrophy of the ligamentum flavum, instability of adjacent vertebrae with spondylolisthesis (anteroposterior slippage of one vertebra on an adjacent one), and narrowing of the lateral recess and intervertebral foramina.

Encroachment of bone or disc may compromise the spinal roots or the spinal cord, resulting in radiculopathy or myelopathy, respectively. Inflammatory mechanisms resulting from exposure of the normally immunologically sequestrated nucleus pulposus, in addition to simple mechanical compression, contribute to the development of radicular symptoms and

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signs. Although plain radiography of the spine may occasionally identify a vertebral fracture or other focal bony pathologic process, it is not an adequate screening investigation for patients with neurologic compromise. Spinal computed tomography (CT) provides detailed views of the bony components of the spine and, when paired with myelography, may demonstrate encroachment onto the thecal space. Spinal magnetic resonance imaging (MRI) is the modality of choice for demonstrating disc and other soft tissue anatomy; MRI can clearly show compression of the roots and spinal cord and does not expose the patient to ionizing radiation. Intramedullary signal abnormalities indicate significant spinal cord injury, but may not correspond closely with clinical severity.

Electromyography (EMG) provides additional, complementary information that helps to distinguish radiculopathy from more peripheral pathology, localize involvement to individual nerve roots, and suggest whether the underlying pathophysiology relates to axonal or demyelinating injury.

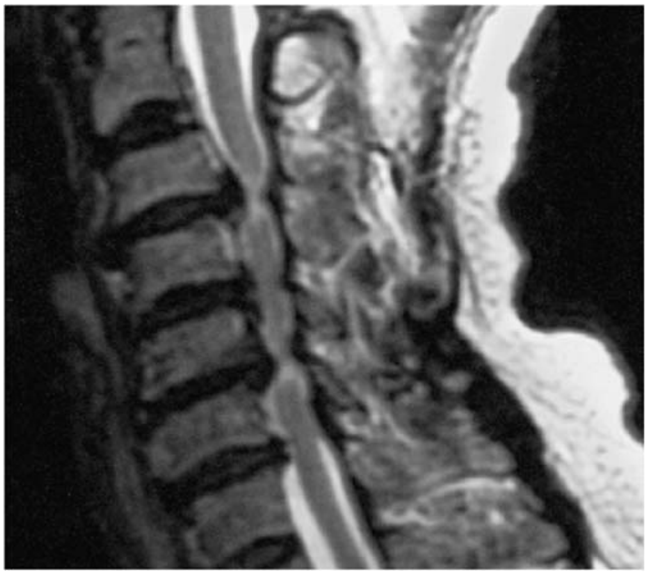

FIGURE 22-1 ■ Cervical spondylosis. Sagittal T2-weighted magnetic resonance imaging of the cervical spine. Multilevel spondylotic disease with spinal stenosis and signal changes in the spinal cord are indicative of myelopathic injury.

Cervical Spondylosis and Disc Disease

In addition to disc degeneration and vertebral spondylosis, the contribution of a congenitally narrow spinal canal, buckling of the ligamentum flavum with neck extension, formation of compressive spondylotic "bars," and ischemic factors have all been proposed as mechanisms leading to neural injury (Figs. 22-1 and 22-2).

Several aspects of the anatomy of this region are important to appreciate: eight pairs of cervical nerve roots are arranged such that a root exits *above* its respective vertebra after leaving its segmental origin in the spinal cord. A lateral disc herniation at the C5–C6 level, for example, will tend to compromise the C6 root. This is the most common level of cervical radicular involvement, followed in order by a herniation at C6–C7 (C7 root) and at C4–C5 (C5 root).

The clinical manifestations of cervical spondylosis can include midline pain over the spine, limited range of movement, referred pain to the ipsilateral neck and arm (often made worse with coughing, straining, or particular positions of the head), and sensory–motor deficits associated with radiculomyelopathy. An acute root injury may occasionally result from rapid movement of the neck with sudden disc herniation; more often, a subacute onset results from progressive foraminal stenosis secondary to spondylosis. Pain tends to be a prominent early symptom, and is often sharp, radiating to a particular dermatome in association with numbness and paresthesias; weakness occurs when motor roots are involved. Corresponding motor, sensory, and reflex changes are found on examination. Single-level disease is seen in 15 to 40 percent of patients, and multilevel disease occurs in 60 to 80 percent.

Cervical myelopathy tends to be a chronic, progressive process, but it may occasionally be abrupt in onset and catastrophic in severity. There are few data to indicate how often cervical spondylotic radiculopathy is eventually associated with myelopathy. Compression of the spinal cord is often heralded by difficulty in walking and may be followed by sensory loss in the lower limbs and the development of urinary frequency and nocturia. A Lhermitte sign may be present. "Numb, clumsy hands" is an unusual symptom complex resulting from upper cord compression.

The natural history of cervical radiculomyelopathy is poorly documented. Good recovery of function frequently follows root injury, especially with a purely demyelinating radiculopathy, from which full recovery within weeks may be expected. Even after partial axonal injury, considerable reinnervation occurs in time. The course of untreated cervical myelopathy varies considerably. Slowly progressive worsening is

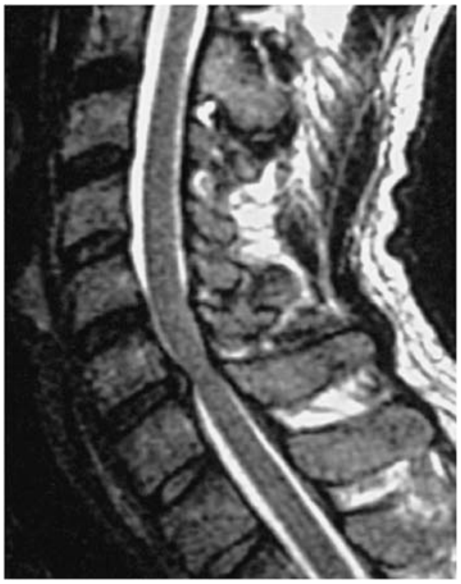

FIGURE 22-2 ■ Cervical disc disease. Sagittal T2-weighted MRI of the cervical spine. A herniated cervical disc is seen to compress the thecal sac at the C6–C7 level.

common, but the myelopathy may remain static for years, improve with conservative measures, or progress rapidly.

Treatment of radiculopathy varies widely, and there is no universally agreed standard of care. Surgery is frequently performed for a variety of indications, despite a lack of large-scale controlled trials comparing surgical and nonsurgical outcomes. A 2010 systematic review found only a single acceptable randomized study of surgery compared with conservative measures.[2] In view of the generally favorable prognosis for recovery of radiculopathy, it is reasonable to embark first on a trial of conservative treatment (a limited period of rest, short-term immobilization with a soft or hard collar, physical therapy, analgesics, anti-inflammatory agents, muscle relaxants) in all patients except those with documented axonal radiculopathy accompanied by progressive muscle weakness. A short course of high-dose oral corticosteroids may help with pain but is not routine. Cervical traction is probably best avoided. The role of local corticosteroid injection (typically fluoroscopically guided, and interlaminar, intralaminar, or transforaminal) is not clearly established; temporary symptomatic relief is often achieved, but the procedure probably has little influence on the ultimate outcome and is not free of complications. Injections may be diagnostically helpful where pain relief is clearly associated with injection at a specific level. The most commonly performed surgery is anterior cervical discectomy and fusion. A posterior approach may be employed if a lateral herniation is present. The role of disc replacement is as yet unclear. In general, surgery is indicated when clinical and electrodiagnostic findings of radiculopathy are congruent with radiologic abnormalities, and either a progressive motor deficit or unremitting pain persists despite an adequate trial of conservative therapy. Acute-onset myelopathy is routinely treated with high-dose intravenous corticosteroids; established myelopathy is usually regarded as a firm indication for discectomy and decompressive laminectomy, with or without fusion; clinical improvement or arrest of progression usually follows, but some 15 to 20 percent of patients continue to deteriorate despite surgery.

Lumbar Disc Disease

Around 80 percent of the adult population will have a functionally significant episode of low back pain over a lifetime; a subset of this group will have discogenic disease. Middle-aged men are most frequently affected. Disc herniation is seen less often in the elderly, probably as a consequence of a less mobile lifestyle and the gradual replacement of the disc material with fibrocartilage. Lumbar spine disease (Fig. 22-3) is frequently an asymptomatic finding on imaging, but may produce a range of symptoms including low back pain, locally referred pain, radiating radicular pain ("sciatica"), and a sensory–motor radicular neurologic deficit. The clinical onset may be spontaneous or associated with an episode of mechanical stress. A flexed posture or a transient increase in the pressure gradient across the dura (e.g., by coughing or sneezing) may exacerbate symptoms.

The site of disc pathology may be marked by local tenderness to palpation or percussion over the spinous processes. The patient may adopt a fixed posture, often tilted away from the affected side, and resist movement. A straight leg raise, with passive flexion of the hip while the leg is extended at the knee, may reproduce the patient's usual back or leg pain in lower lumbosacral radiculopathy. The pattern of neurologic deficit will allow identification of the affected root.

Most lumbar disc pathology involves the L4–L5 and L5–S1 interspaces. Disc abnormalities at L1–L2,

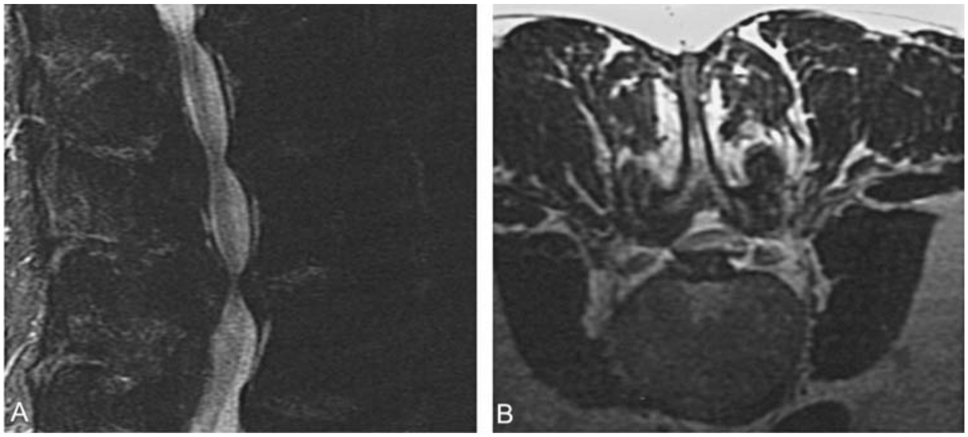

FIGURE 22-3 ■ Degenerative disease of the lumbar spine with spinal stenosis. Sagittal, *A*, and axial, *B*, T2-weighted MRI of the lumbar spine. Multilevel discogenic disease is apparent in the lumbar spine on the sagittal view. Disc material is seen compressing the anterior aspect of the thecal sac on the axial image.

L2–L3, and L3–L4 are rare, accounting for less than 5 percent of patients. Lumbar disc protrusions are most often posterolateral and affect either descending or exiting nerve roots; they typically cannot result in myelopathy because the spinal cord ends above the L1–L2 interspace. The roots are located posterolaterally at the intervertebral foramen and pass through this aperture in a superior position; therefore a disc protruding at the same level will tend to pass underneath the root exiting at the same interspace, often compressing the root of the segment immediately below. An L4–L5 disc, for example, will usually compromise the L5 root and leave the L4 root unaffected. There are exceptions to this rule—clinical assessment should always allow that a nerve root can be compromised at any point in its intraspinal course.

A large central disc may produce bilateral radicular signs or occasionally result in acute cauda equina syndrome characterized by flaccid paralysis, lower-limb areflexia, or urinary and fecal incontinence. Acute cauda equina syndrome is a surgical emergency and, even when managed promptly, carries a poor prognosis for neurologic recovery. Chronic lumbar canal stenosis may lead to neurogenic claudication (see later).

The differential diagnosis for these symptoms is wide. For patients who present with acute (duration of less than 3 months) low back pain, the emphasis of the initial assessment is on exclusion of serious underlying pathology. Neoplastic, infectious, and traumatic causes are important to identify and require specific treatment. Otherwise, conservative measures (limited bed rest, regular graded exercise, analgesic and anti-inflammatory medication, physical therapy, and the use of local corticosteroid injections in selected patients) without further investigation represent the most appropriate initial management. When there is no improvement, further investigation is indicated.

The natural history of uncomplicated lumbar disc disease is usually one of eventual disc resorption with improvement of symptoms. Despite this generally good prognosis, lumbar disc surgery represents the most common elective surgical procedure involving the nervous system. The traditional approach is resection of the intervertebral disc and fusion of the vertebrae above and below. Other approaches include intervertebral disc replacement and electrothermal and radiofrequency therapy, but their role is yet to be established. Surgery is indicated when a motor deficit (by clinical examination or EMG) is worsening despite conservative management. There is much debate regarding the efficacy of surgery for other patients, and few prospective data are available to help predict which patients are likely to be treated successfully.

LUMBAR SPINAL STENOSIS AND NEUROGENIC CLAUDICATION

Stenosis of the lumbar spinal canal (as well as stenosis of the lateral recess and neuroforamen) is frequently asymptomatic and found incidentally on imaging studies. Boden and colleagues found that 21 percent of asymptomatic adults older than 60 years had lumbar spinal stenosis on MRI.[1] Other patients may complain of low back pain and neurogenic claudication, classically described as discomfort and aching pain in the lower back, buttocks, and legs that is precipitated by walking and relieved by sitting. Patients may experience numbness, paresthesias, weakness, or a sense of heaviness in the legs, usually bilaterally and asymmetrically. Up to 11 percent of patients present with bladder and sexual dysfunction. Sitting for some time will usually relieve symptoms sufficiently to allow further walking. Relief of symptoms with flexion of the spine is the reason that it is often easier to walk up an incline than on a level surface, ride a bike, or lean on a grocery cart. Neurogenic claudication is usually of gradual onset and, once established, results in symptoms that may become disabling, but tends not to be associated with a progressive neurologic deficit, although single or multiple root deficits may occur. Abnormalities on clinical examination may become more apparent after exercise.

Pathogenesis is incompletely understood but is likely to include both mechanical compression and ischemia of the cauda equina leading to neurapraxia with transient conduction failure and clinical and electrophysiologic changes. The anatomic substrate is most commonly that of progressive, chronic, degenerative lumbar spine disease (disc protrusion, osteophytosis, and hypertrophy of the ligamentum flavum) on a background of a congenitally or developmentally narrow lumbar spinal canal, including conditions such as spina bifida and achondroplasia. Occasionally, disease of the spine or mass lesions are responsible.

Extension of the spine decreases, and flexion increases, the caliber of the spinal canal. Diagnosis requires recognition of the highly characteristic history together with radiologic evidence of lumbar spinal stenosis. There is no consensus on measurement: methods make use of anteroposterior diameter, cross-sectional area, and vertical extent of stenosis. There is also poor correlation between the degree of stenosis and clinical manifestations. Electrodiagnostic studies may show prolongation of minimum F-wave and H-reflex latencies, but are mainly useful to document associated radiculopathy. In contrast, vascular claudication typically causes burning pain in the calves when walking and is usually accompanied by evidence of circulatory insufficiency in the legs. A variety of other neurologic conditions may occasionally produce pseudoclaudication: these include multiple sclerosis and spinal cord arteriovenous malformation.

Many patients with lumbar spinal stenosis find that they can remain mobile within the specific constraints of their symptoms with conservative measures. Surgery aims to relieve symptoms and improve function and is appropriate where progressive disability or intractable pain is present. Of patients initially opting for conservative therapy, about 30 percent will eventually elect to have surgery. Surgery likely benefits some patients, but the literature provides few controlled data comparing it with conservative treatment. Further, benefit may not persist, and surgery at one level may lead to degeneration in adjacent vertebrae, leading to a progressive deficit. Decompressive laminectomy at one or several levels is typically performed with discectomy or simple foraminotomy, with or without fusion. Surgery is warranted if neurogenic claudication is progressive, significantly limits activities of daily living, or becomes intolerable. Surgery is usually elective, but may need to be expedited in the case of progressive weakness or cauda equina syndrome. Fusion with or without instrumentation is more frequently employed when there is associated spondylolisthesis. Interspinous decompression with placement of a spacer (e.g., X-STOP) between the spinous processes, preventing narrowing of the canal with extension, is a less-invasive technique that is sometimes employed.

OSTEOPOROSIS

Osteoporosis is a disorder characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk. It is the most common bone disease. It results in 1.5 million fractures per year in the United States.[3] One-half of Caucasian women and around 20 percent of Caucasian men will experience an osteoporotic fracture. Despite this, only about a quarter of older woman who have an osteoporotic fracture are treated for osteoporosis in the 6 months following the fracture. Any neurologic disorder that impairs strength or balance leading to decreased mobility and an increased risk of falls is a risk factor for osteoporosis (Table 22-1). Patients with spinal cord injury are particularly prone to severe osteoporosis and nontraumatic fractures. Neurologic patients share common risk factors with

TABLE 22-1 ■ Neurologic Diseases Associated with Osteoporosis and Increased Fracture Risk

Alzheimer disease	Amyotrophic lateral sclerosis
Parkinson disease	Poliomyelitis
Spinal cord injury	Muscular dystrophy
Epilepsy and anticonvulsant use	Glycogen storage diseases
Stroke and anticoagulant use (heparin)	Gaucher disease
Multiple sclerosis	Menkes steely hair syndrome
	Riley–Day syndrome

elderly patients for osteoporosis, such as disuse and lack of exercise, being homebound, vitamin D deficiency, and poor diet. Parkinson disease is an independent risk factor. Tobacco and alcohol use are also risk factors for osteoporotic fractures.

There is growing interest in "neuroskeletal research" of the central nervous system (CNS) regulation of bone remodeling. Leptin is a peptide secreted by adipocytes that regulates appetite and energy metabolism by binding to a hypothalamic leptin receptor. Its effect on bone formation is through induction of the sympathetic nervous system. Osteoblasts in the bone marrow reside next to sympathetic neurons and express β_2-adrenergic receptors; catecholamines increase osteoblast proliferation and differentiation (bone formation) and increase bone resorption, with a resulting decrease in bone mass. There also is evidence of a circadian variation for bone remodeling.

The spine is the most frequent osteoporotic fracture site, accounting for approximately 1.4 million clinically detected fractures annually worldwide.[4] Low thoracic and high lumbar vertebral fractures are the most common. There is a 10-fold increased risk of a second vertebral fracture in these patients. About 25 percent of vertebral fractures occur from falls, but the majority are triggered by trivial activity such as bending, lifting a light object, or getting out of bed.

Most vertebral fractures are painless and only around 30 percent come to medical attention. Less than 10 percent result in hospital admission. Symptomatic patients usually present with acute low back pain localized to the site of the fracture, but sometimes diffuse and nonlocalizing. Radiating pain into the lower extremities is uncommon and usually does not correspond to a specific lumbar root pattern. Straining and local percussion typically increase the pain. The patient may not be able to bear weight initially, and symptoms often improve when lying down. There are typically no neurologic symptoms or signs.

Plain radiographs of the spine are the study of choice to document the presence of vertebral fracture. The most widely accepted radiologic definition of vertebral compression-fracture is a decrease of 15 to 25 percent in the anterior, central, or posterior height of a vertebral body compared with adjacent normal vertebrae or a population reference. The diagnosis can be confirmed by bone scan or CT when radiographs are equivocal.

The optimal treatment of acute osteoporotic vertebral fractures without neurologic compromise is uncertain. Prolonged bed rest may accelerate the underlying osteoporosis, so analgesics, local heat alternating with cold application, and mobilization with physical therapy and hydrotherapy are recommended. Rigid external support can prevent failed union of severe vertebral fractures when used in the first 6 months. Narcotics are occasionally required for pain, and calcitonin may provide relief in the acute phase. With persistent pain, an intercostal nerve block or epidural corticosteroid injection may be helpful. Vertebral augmentation can be done with vertebroplasty, a balloon implant (balloon kyphoplasty), or vertebral body stenting. Vertebroplasty is a technique that involves injection of polymethylmethacrylate into a fractured vertebral body. Compared to conservative treatment for acute painful fractures, it shows greater pain relief, functional recovery, and health-related quality of life.[4] Asymptomatic cement leaks are a potential side effect, and uncommon severe adverse events include radiculopathy due to cement leakage, new fractures of adjacent vertebrae, and osteomyelitis. Vertebral body stenting with an expandable metallic implant is another minimally invasive technique that may help preserve vertebral body height and prevent spinal deformity.

Preventive treatments for osteoporosis are essential to reduce the number of vertebral fractures in postmenopausal women and the elderly. Detailed recommendations for evidence-based osteoporosis prevention including exercise (balance, resistance, weight bearing, and muscle strengthening), fall prevention strategies, risk factor modulation, calcium and vitamin D supplementation, bisphosphonates, hormone replacement, selective estrogen-receptor modulators, desosumab, teriparatide, abaloparatide, romosozumab, and calcitonin are summarized elsewhere, including side effects and treatment holidays.[3]

The association between vertebral fractures and chronic back pain is unclear. In patients with osteoporosis and vertebral fractures, the presence and severity of back pain correlate with the number of collapsed thoracic vertebrae and the degree of kyphosis. Neurologic complications are uncommon and include myelopathy, cauda equina syndrome, and lumbosacral radiculopathy. Spinal CT or MRI reveals violation of the posterior cortex of the vertebral bodies (burst fracture) with retropulsion of bone into the spinal canal. The most common location is the thoracolumbar junction. Lower-extremity symptoms may develop from 10 days to 1.5 years after the onset of acute spine pain, owing to extension of vertebral fracture. The etiology is thought to be late collapse of the vertebral body due to disruption of the microcirculation and aseptic necrosis. Severe kyphosis may be a risk factor for progression of vertebral fracture and neurologic compromise.

The best operative approach for those with neurologic deficits is not known. Goals include improvement of the deficit, correction of the deformity, and stabilization of the spine. Clinical results are mixed, ranging from marked improvement to worsening of function with significant postoperative mortality. The approach used is often guided by the presence of intervertebral instability, the degree of kyphosis, and the occurrence of progressive neurologic deficits. Postoperative bracing may reduce the rate of instrumentation failure. Conservative management in some cases can result in significant recovery over months.

Occasionally, patients with vertebral fracture have purely radicular symptoms, with pain radiating into the lower extremity that worsens with change in position or on standing. There may be dermatomal sensory loss and weakness in muscles referable to that root. There may be a higher association of radiculopathy with inferior-type vertebral fractures. There can be substantial or complete resolution of symptoms following vertebroplasty.

OSTEOMALACIA

Osteomalacia is a metabolic bone disorder characterized by defective mineralization, which results in the accumulation of unmineralized matrix or osteoid in the skeleton. Normal bone mineralization requires adequate circulating levels of vitamin D metabolites, a normal supply of minerals, and optimal osteoblast function. The most common cause of osteomalacia is vitamin D deficiency. Other causes are listed in Table 22-2. Reduced cutaneous production of vitamin D is a concern in the elderly who are institutionalized or housebound, and in postmenopausal women. Increased time indoors, sunscreen, and the use of ultraviolet-protective glass and clothing contribute to hypovitaminosis D. Dark-skinned individuals require four to five times more sun exposure than light-skinned people. Dietary sources of vitamin D are limited (wild oily fish, egg yolk, codliver oil, and fortified food). Malabsorption results in decreased absorption of vitamin D, increased catabolism of vitamin D metabolites, and malabsorption of calcium or phosphate. Malabsorption from gastric bypass surgery for morbid obesity is

TABLE 22-2 ■ Causes of Osteomalacia

Vitamin D Deficiency
Reduced cutaneous production
Poor nutrition
Malabsorption
Abnormal Vitamin D Metabolism
Liver disease
Drugs (anticonvulsants)
Hereditary defective 25-hydroxycholecalciferol synthesis
Defective 1,25-dihydroxycholecalciferol synthesis
Renal failure
Vitamin D-dependent rickets type I (1α-hydroxylase deficiency)
Resistance to the Action of Vitamin D
Vitamin D-dependent rickets type II
Hypophosphatemia
Phosphate-binding antacids
X-linked hypophosphatemia
Oncogenic osteomalacia
Fanconi syndrome
Renal tubular acidosis
Bone Toxins
Bisphosphonates
Aluminum
Fluoride
Hypophosphatasia
Fibrogenesis Imperfecta Ossium

emerging as a leading cause of vitamin D deficiency in the United States.

The prevalence of low 25(OH)D levels ($<$20 ng/mL) is 36 percent in healthy young adults aged 18 to 29 years, 42 percent in black women aged 15 to 49 years, 41 percent in outpatients aged 49 to 83 years, and up to 57 percent in general medicine inpatients in the United States.[5] It is especially prevalent in nonelderly, ambulatory primary-care patients with persistent, nonspecific musculoskeletal pain refractory to standard pharmaceutical agents. Current recommendations in North America are that all adults supplement with vitamin D_3 600 IU/day and that those in at-risk groups or older than 70 years should take 800 IU/day. The global consensus is 400 IU daily for all infants until 12 months, 600 IU daily for women during pregnancy, and that all groups beyond 12 months receive 600 IU daily via diet or supplementation.[6] Food fortification is also recommended as a prevention measure.

The classic clinical features of osteomalacia include musculoskeletal pain, skeletal deformity, muscle weakness, and symptomatic hypocalcemia. The early symptoms are vague. Bone pain is invariably present, symmetric, and especially prominent in the spine, ribs, pelvis, and lower extremities. The pain is worse with muscle strain, weight bearing, or pressure, but persists with rest. Minimal pressure with the thumb or forefinger on the sternum, ribs, pelvic girdle, or anterior tibia can reproduce the pain on physical examination; it is postulated that collagen-rich osteoid deposited on the periosteal surface of the skeleton may become swollen, putting outward pressure on the periosteal covering that is innervated with nociceptors. These patients are often misdiagnosed as having fibromyalgia, chronic fatigue syndrome, or myositis, and treated inappropriately with nonsteroidal anti-inflammatory drugs (NSAIDs).

Proximal myopathy is common. The limb-girdle muscles are the most affected and result in a waddling gait, Gowers sign, or inability to walk. The proximal upper extremities and neck flexors are occasionally involved; distal weakness is rare, and bulbar and sphincter muscles are spared. Weakness is accompanied by myalgias and muscle atrophy, although the atrophy is often out of proportion to the degree of weakness. There is no known direct effect of vitamin D on muscle but the degree of weakness may be related in part to hypophosphatemia. Deep tendon reflexes are often brisk and the combination of weakness, atrophy, and hyperreflexia can be mistaken for amyotrophic lateral sclerosis. Vitamin D deficiency may contribute to age-related muscle weakness and falls, and vitamin D supplementation for elderly ambulatory and institutionalized individuals reduces the risk of falls.

Osteomalacia in childhood or nutritional rickets has a rising incidence globally, with short stature, bowing of the legs, and widening of the metaphyses, which leads to a "rickety rosary" appearance in the ribs. Muscle weakness results in hypotonia and motor delay. Other clinical features include swelling of the wrists and ankles, bone pain, restlessness, irritability and delayed tooth eruption. In older children and adolescents, rickets can manifest during periods of rapid growth. Rickets results in an increased risk of fracture.

Maternal vitamin D deficiency is passed on to the fetus and if severe can result in hypocalcemic complications in the newborn that include tetany, seizures, and dilated cardiomyopathy, with increased mortality. Premature closure of the sagittal cranial sutures may result in craniotabes and, if severe, hydrocephalus.

Vitamin D modulates the immune system by decreasing the proliferation of proinflammatory T lymphocytes and regulating the production of cytokines. There is an association between high vitamin D levels and a reduced risk of developing multiple sclerosis, but the impact of vitamin D levels on the severity and progression of multiple sclerosis remains unclear. Supplementation in this population with 1,000 IU/day is recommended to reach immune-modulating serum levels of vitamin D (30 ng/mL or 75 nmol/L). Vitamin D is also involved in brain development and adult brain function. Vitamin D receptors are present in almost all brain structures, in neuronal and glial cell types, and vitamin D functions as a neurosteroid. There is growing evidence that vitamin D deficiency increases the risk of Parkinson disease, cerebrovascular disease, epilepsy, and dementia, including Alzheimer disease.

Radiologic features of osteomalacia include cortical thinning of bone, cortical striations in the metacarpals and phalanges, and osteopenia. The most characteristic feature is the presence of Looser zones, which are lucent bands adjacent to the periosteum that may represent unhealed stress fractures and most commonly occur in the ribs, pubic rami, and outer borders of the scapulae. Biochemical abnormalities may be minimal and vary with the cause of osteomalacia. A classic triad is hypocalcemia, hypophosphatemia, and increased serum alkaline phosphatase. Serum 25(OH)D is the major circulating metabolite of vitamin D and reflects input from cutaneous synthesis and dietary intake. A minimum level of 20 ng/mL (50 nmol/L) is necessary to satisfy the body's vitamin D requirement, but a level of 30 to 50 ng/mL (75 to 125 nmol/L) is preferred. Despite clinical evidence of myopathy, the serum creatine kinase level is typically normal. Parathyroid hormone levels may be elevated. Hypocalcemia is usually present when osteomalacia is associated with renal failure, but the serum phosphate is normal or high because of reduced urinary excretion.

EMG may be normal in patients with weakness but most patients show small, short-duration, polyphasic motor unit action potentials in proximal muscles, without abnormal spontaneous activity. The findings on muscle biopsy are nonspecific and include type II atrophy.

Treatment of osteomalacia includes ultraviolet irradiation (UV-B wavelength of 290 to 315 nm) and vitamin D replacement. An oral dose of 50,000 IU/week of vitamin D_2 for 8 weeks, with monitoring of 25 OH) D and parathyroid hormone levels, should occur in those with vitamin D deficiency. In some cases, a second once-weekly 8-week course of 50,000 IU of vitamin D_2 may be necessary to boost 25(OH)D levels into the desired range of more than 30 to 50 ng/mL (75 to 125 nmol/L). For patients prone to developing vitamin D deficiency, after correction of any deficiency, the administration of 50,000 IU every 2 weeks will maintain a vitamin D-sufficient state. An alternative to vitamin D_2 is vitamin D_3 1000 IU/day. Calcium and magnesium supplements are also recommended concurrently. Complications of treatment are uncommon, but include hypercalcemia, renal dysfunction, and increased long bone and hip fractures as pain improves before bone mass and strength are restored. The bone pain, symptoms of hypocalcemia, and proximal weakness often resolve completely over weeks to months with treatment, but deformities persist despite remodeling of the bone. Global recommendations for the treatment of nutritional rickets is 2,000 IU per day for 3 months, together with oral calcium 500 mg daily.

Hypophosphatemic osteomalacia has different neurologic complications than other causes of osteomalacia. The most common form is an X-linked syndrome with hypophosphatemia, osteomalacia, short stature, and the eventual development of new bone at various body sites associated with mutations in the *PHEX* gene. The proximal myopathy seen with other forms of osteomalacia does not occur. Rarely, myelopathy develops as a result of intraspinal new bone formation. The mid- and low thoracic spine is the predominant site of involvement, but the cervical spine may also be affected. The onset of symptoms is acute or insidious with paresis, sensory loss, and, less frequently, bladder symptoms. Symptoms can be intermittent and involve multiple levels of the spinal cord, mimicking multiple sclerosis. A rare autosomal dominant form is associated with a mutation of the fibroblast growth factor 23 gene (*FGF23*). The clinical features are similar to the X-linked form but there is variable penetrance with variable age of onset and it may resolve later in life. An autosomal recessive form is defined by mutations in the dentin matrix protein 1 gene (*DMP1*).

CT of the spine shows enlargement of the facet joints, thickening of the laminae, and ossification within the spinal canal, resulting in severe central stenosis. Surgery is difficult due to thickening of the bone and adherence of the dura to the ligamentum flavum but can result in improvement or resolution of deficit. Treatment includes an oral neutral phosphate along with 1,25-dihydroxyvitamin D (calcitriol). Excess vitamin D replacement can cause hypercalcemia, leading to soft tissue calcification. Serum calcium levels should therefore be measured monthly. Diuretics such as amiloride or hydrochlorothiazide enhance calcium reabsorption and can reduce the risk of nephrocalcinosis.

OSTEOPETROSIS

Osteopetrosis refers to a rare group of sclerosing bone disorders characterized by a generalized increase of skeletal bone mass due to a defect in osteoclastic bone resorption.[7] At least 10 genes have been identified that result in a failure of osteoclast development or function (Table 22-3) and most forms result from late endosomal trafficking defects that prevent osteoclast ruffled-border formation. With more widespread genetic testing, new forms of osteopetrosis in single patients have been described with *TRAF6*, *LRRK1*, *MITF*, *CSF1R*, and *RELA* mutations. In osteopetrosis, the development of the marrow cavity is delayed or absent, and impaired bone modeling

TABLE 22-3 ■ Inheritance of Osteopetrosis

Disease	Inheritance	Gene	Protein
Malignant (infantile) form	AR	*TCIRG1*	Subunit of V-ATPase pump
	AR	*CLCN7*	Chloride channel
	AR	*OSTMI*	Osteopetrosis-associated transmembrane protein
	AR	*SNX10*	Sorting nexin-10 (protein cargo sorting)
	AR	*TNFSF11*	Receptor activator for nuclear factor κB ligand (osteoclast poor)
	AR	*TNFSF11A*	Receptor activator for nuclear factor κB (osteoclast poor)
Intermediate form	AR	*CLCN7*	Chloride channel
	AR	*PLEKHMI*	Pleckstrin homology domain containing family M, member I
Osteopetrosis with renal tubular acidosis	AR	*CAII*	Carbonic anhydrase II
Late-onset form	AD	*CLCN7*	Chloride channel
Asymptomatic (osteopoikilosis)	AD	*LEMD3*	LEM domain-containing 3
Osteopetrosis with ectodermal dysplasia and immune defect (OLEDAID)	X	*NEMO*	IκB kinase complex component
X-linked osteopetrosis	X	*NEMO*	NF-κB essential modulator
Leukocyte adhesion deficiency syndrome and osteopetrosis (LAD-III)	AR	*FERMT3*	Kindlin-3
	AR	*ColDAG-GEFI*	Calcium and diacylglycerol-regulated guanine nucleotide exchange factor I

AD, autosomal dominant; AR, autosomal recessive; X, X-linked.

during longitudinal growth results in a broad cylindrical shape at the ends of the long bones. These bones become brittle, with an increased susceptibility to fracture. Radiographic features are needed to make the diagnosis and include diffuse sclerosis, bone modeling defects at the metaphyses of long bones, "bone in bone" appearance of the vertebrae and phalanges, as well as focal sclerosis of the skull base, pelvis, and vertebral endplates. The most serious complications of the osteopetroses affect the nervous system and hematopoietic system. Cranial nerves, blood vessels, and the spinal cord are compressed by either gradual occlusion or lack of growth of skull foramina. The severity of osteopetrosis ranges from neonatal onset with life-threatening complications to asymptomatic.

Malignant osteopetrosis presents during infancy and is the most common form of childhood osteopetrosis. Inheritance is autosomal recessive and nearly 70 percent of mutations are in the osteoclast vacuolar proton pump and the H^+-Cl^- exchange transporter.[7] The course is severe, with a high mortality rate in early childhood without treatment. Its incidence is approximately 1 in 300,000 births. Neurologic involvement occurs frequently and includes hearing loss, optic atrophy with blindness, nystagmus, strabismus, trigeminal neuropathies, facial paralysis, dysarthria, hydrocephalus, intracranial hemorrhage, cognitive dysfunction, and tetanic convulsions. Hydrocephalus is due to obstruction of the venous outflow at the cranial foramina and to inadequate circulation of cerebrospinal fluid (CSF) as a consequence of thickening of the bones of the skull. Posterior fossa crowding and cerebellar tonsillar herniation may occur. Cranial nerve involvement relates to bony encroachment, and may necessitate decompression of the optic, facial, or vestibulocochlear nerves. Retinal degeneration has been described in some patients and is another cause of visual loss; the most frequent sign of early damage is a change in latency of the visual evoked potential. Baseline brain MRI with special attention to the optic foramina is recommended in these patients, followed by CT of the head if there is evidence of cranial nerve involvement.

Non-neurologic features include short stature, dental caries, and frequent fractures. The constricted bone marrow cavity cannot support adequate hematopoiesis, resulting in hepatosplenomegaly, thrombocytopenia, anemia, and infectious complications, particularly osteomyelitis. Hypocalcemia and rickets also occur. "Osteopetrorickets" occurs with the *TCIRG1* mutation due to low gastric acidity.

First-line treatment includes calcium and vitamin D supplementation to prevent tetanic seizures and treat secondary hyperparathyroidism. High-dose calcitriol is no longer recommended as evidence of clinical benefit is lacking. Interferon-γ1b, which reduces the number of infections and increases bone resorption and the size of bone marrow spaces, has early evidence of efficacy in malignant osteopetrosis. Bone marrow failure is treated with transfusions of red blood cells (if the anemia is symptomatic) and platelets. Allogenic hematopoietic cell transplantation is currently the only therapy capable of producing long-term benefit in children with autosomal recessive osteopetrosis with the exception of those with mutations of the *TNFRSR11* gene or if neurodegeneration is present (*OSTM1* and many *CLCN7* mutations). Early transplant (before 3 months) limits neurosensory defects and impaired bone growth and results in reconstitution of normal hematopoiesis and neutrophil function. Outcomes are improved with an HLA-identical donor. Significant risks include a high frequency of graft rejection, veno-occlusive disease, and severe pulmonary hypertension. Corticosteroids are recommended as second-line therapy in children when hematopoietic cell transplantation is not appropriate. Optic nerve decompression and optic sheath fenestration can improve visual function if performed early. There is some limited support for facial and acoustic nerve decompression to preserve facial strength and hearing, respectively.

Neuropathic autosomal-recessive osteopetrosis is a rare form with nontetanic seizures, developmental delay, hypotonia, retinal atrophy, and sensorineural deafness and is associated with the *OSTM1* mutation. There is primary neurodegeneration, and brain MRI abnormalities include delayed myelination, diffuse progressive cortical and subcortical atrophy, and bilateral atrial subependymal heterotopias.

Intermediate autosomal-recessive and autosomal-dominant osteopetroses (*CNCL7* mutation) have a less severe course and have few neurologic complications, with the uncommon exception of facial weakness and visual and hearing loss due to cranial nerve compression. Frequent fractures are the most common clinical feature.

Carbonic anhydrase II deficiency (marble brain disease) is an autosomal-recessive disorder resulting in osteopetrosis, renal tubular acidosis, and cerebral calcification. It presents in late infancy or early childhood with developmental delay, cognitive abnormalities, short stature, failure to thrive, a large cranial vault, weakness, cranial nerve compression, and a history of multiple fractures. Patients may have apathy, global hypotonia, or muscle weakness that is attributed to acidosis and diminished blood levels of potassium from renal tubular acidosis. Rarely, episodic hypokalemic weakness occurs. Many patients develop optic atrophy associated with reduced optic canal size on imaging. Less common cranial nerve deficits are facial palsy and deafness.

Metabolic abnormalities include a metabolic acidosis with a persistently positive urinary anion gap without renal failure. Anemia and splenomegaly may be present. Plain radiographs show increased density in the long bones, vertebral bodies, pelvis, and skull. Cranial CT or MRI shows thickened skulls with small or absent paranasal sinuses. Symmetric brain calcifications are present involving the basal ganglia, thalamus, gray–white junction (with a frontal lobe predilection), or some combinations of these sites. The amount of calcification progresses over time but does not correlate with the degree of cognitive abnormalities in these patients. The diagnosis can be made through an erythrocyte assay or by molecular probes for carbonic anhydrase II. Prenatal diagnosis requires direct carbonic anhydrase II gene sequencing. Patients are treated for acidosis with bicarbonate and Na/K citrate. Although the impact of treatment on the natural progression of the bone and neurologic features is unclear, there may be some effect in delaying the development of hearing loss and extramedullary hematopoiesis.

Infantile neuroaxonal dystrophy is a rare autosomal-recessive disorder due to a mutation of the *PLA2G6* gene, with widespread accumulation of neuroaxonal spheroids in the cortex, basal ganglia, brainstem, spinal cord, and peripheral nerves. It has been reported in association with osteopetrosis. It presents during the first 2 years of life with weakness, hypotonia, rigidity, pyramidal signs, cerebellar ataxia, diminished pain sensation, optic atrophy, and mental impairment, accompanied by hypocalcemia, hypomagnesemia, severe anemia, thrombocytopenia, hepatosplenomegaly, jaundice, and metabolic acidosis. Peripheral nerve signs such as diminished muscle stretch reflexes may be present, and the combination of central and peripheral signs is a clue to the diagnosis. Neuroimaging shows agenesis of the corpus callosum, ventriculomegaly, and cerebellar atrophy with hyperintensity on T2-weighted images. Electrodiagnostic findings are consistent with a distal axonal sensorimotor neuropathy. This form of osteopetrosis is fatal within the first few years of life.

PAGET DISEASE OF BONE

Paget disease is a focal disorder of bone turnover in which there is excessive bone resorption coupled with abnormal new bone formation, resulting in architecturally disorganized and mechanically weak bone. It has a predilection for the axial skeleton and involves the cervical spine in 15 percent, thoracic spine in 44 percent, lumbar spine in 54 percent, and skull in 42 percent of cases.[8] The prevalence increases with age, and the disorder is found primarily in Caucasians, although in recent years its incidence and severity have decreased.[9] There is a family history in 15 percent of patient with an autosomal-dominant pattern of inheritance. The etiology is incompletely understood but probably relates to a combination of genetic susceptibility and environmental factors, although the only disease-causing gene identified to date is sequestosome 1 (*SQSTM1*), found in one-half of affected families and 9 percent of sporadic cases. Patients with *SQSTM1* mutations have earlier onset and more severe disease.

Most patients with Paget disease are asymptomatic. The most common presentation in symptomatic patients is local bone pain coupled with overlying skin warmth due to increased bone microvasculature. The pain is continuous and worse at rest and at night. There may be obvious deformity of the bones, and skeletal complications include osteoarthritis, fractures, and sarcomatous changes.

Plain radiographs may show lytic lesions early in the disease; as the disease progresses, a chaotic, crisscross pattern with thickened cortical and trabecular bone is seen, sometimes accompanied by pseudofractures. The most sensitive metabolic marker of Paget disease is total serum alkaline phosphatase, which is elevated in almost all untreated patients. Procollagen-1N-propeptide is a good marker of bone turnover in Paget disease.

Treatment depends on the location and activity of the disease.[9] Asymptomatic patients usually do not require treatment, and pain is the only symptom for which there is proven benefit from treatment. Bisphosphonates (e.g., alendronate, tiludronate, risedronate, pamidronate, and zoledronic acid) produce a marked and prolonged inhibition of osteoclast function and are currently the first-line therapy. These agents reduce or normalize serum total alkaline phosphatase levels. Zolendronic acid may be superior to risedronate for treating symptoms, and patients with milder disease may only require a single intravenous treatment. It is important to correct vitamin D deficiency prior to intravenous bisphosphonate treatment to prevent hypocalcemia. Calcitonin or possibly the osteoclast inhibitor denusumab can be used in patients in whom bisphosphonates are contraindicated. Analgesics, anti-inflammatory drugs, and antineuropathic drugs may be helpful for bone pain.

Neurologic involvement is rare and occurs as a result of the close anatomic relationship of bone with the brain, spinal cord, cauda equina, spinal roots, and cranial nerves.[8] Compression from expanding bones or fracture is the most common cause of neurologic dysfunction. Less common causes include ossification of extradural structures, osteosarcoma, and epidural hematoma. Ischemia of the nervous system may occur occasionally due to compression of vascular structures or a vascular steal phenomenon; measurement of skeletal blood flow demonstrates that the affected bone receives up to 18 percent of cardiac output compared with 5 percent in normal bone.[8]

Other neurologic complications of cranial disease include headache, epilepsy, dementia, brainstem and cerebellar dysfunction, and cranial neuropathies. Headache is severe, frequently occipital, and worsened by coughing, sneezing, or straining. Dementia may result from direct compression of the cerebral hemispheres or from hydrocephalus. Epilepsy may occur from direct compression of the cerebral cortex.

In advanced cranial disease, there is softening of the skull base that can result in an anatomic lowering of the skull onto the upper cervical vertebrae (i.e., basilar invagination), leading to obstructive hydrocephalus and compression of the cerebellum, lower cranial nerves, corticospinal tract, and upper cervical nerves. The severity ranges from asymptomatic to tonsillar herniation and death. The typical presentation is that of slowly progressive ataxia, vertigo, tinnitus, dysphagia, dysarthria, and occipital headache. Vertebrobasilar insufficiency as well as obstructed venous return may lead to cerebrovascular compromise. An unusual picture resembling amyotrophic lateral sclerosis sometimes occurs in association with cervical cord involvement.

Any of the cranial nerves may be affected with Paget disease, but the olfactory and auditory nerves are involved most commonly. Hearing loss occurs in one-third of patients. It may be neuronal, conductive, or of mixed type. The cochlea is the most common site of involvement. The optic nerve may be affected at the optic foramen by compression of the vasa nervorum; patients present with diminished vision or blindness, retinal hemorrhages, choroiditis, optic atrophy, papilledema, and angioid streaks. The nerves controlling eye movements are vulnerable as they pass through the superior orbital fissure, leading to diplopia and abnormal pupillary responses. Exophthalmos from direct impingement of the extraocular muscles themselves occurs rarely. Trigeminal nerve involvement can lead to facial numbness and trigeminal neuralgia. Involvement of the facial nerve may result in hemifacial spasm or facial paresis.

Osteosarcoma of the skull occurs in less than 1 percent of patients with Paget disease.[8] It usually presents as a partially fluctuant and locally painful skull mass with rapid neurologic deterioration in the setting of long-standing disease. The prognosis is poor despite radiation therapy and surgery. Epidural hematomas can cause acute compression of the spinal cord or brain and are related to the increased blood flow to bone and increased risk of pathologic fractures. The prognosis in these cases is also poor, owing to excessive bleeding during surgery.

The spine is the second most common site of involvement in Paget disease and, prior to effective treatment with bisphosphonates, resulted in symptoms of spinal stenosis in 26 percent of patients.[8] Mechanisms of neurologic compromise include: (1) direct compression of the spinal cord, cauda equina, or nerve roots by enlarged vertebrae (most commonly) or expansion of facet joints; (2) pathologic fractures or subluxation; (3) ossification of extradural structures; (4) diversion of the local blood supply to highly vascular bones; and (5) pressure on vessels as they pass through the intervertebral foramina. Sarcomas or epidural hematomas are rare. The onset of continuous severe spinal pain and rapid neurologic deterioration should raise concern of osteosarcoma.

Back pain often occurs in patients with involvement of the spine. Osteoarthritis is prevalent in this elderly population and can be difficult to distinguish from Paget disease as the cause of pain. Other changes in the spine include thickening of the pedicles and laminae, flattening of the vertebral bodies, and encroachment of the spinal canal by osteophytes. Involved vertebrae are increased in width and reduced in height. The most commonly involved levels are the upper and lower cervical, low thoracic, and midlumbar regions. Of those with involvement of the spine demonstrated on plain radiographs, two-thirds will have evidence of spinal stenosis by CT and half of those patients will have clinical evidence of myelopathy or a cauda equina syndrome. There is no association between the number of vertebrae involved and presence of symptoms.

Low back pain may respond to treatment with bisphosphonates. Pain that does not respond after 3 months should be treated with NSAIDs. Improvement or reversal of symptoms of spinal stenosis has been demonstrated with mithramycin, etidronate, pamidronate, and clodronate. Prompt surgical decompression is appropriate for patients who do not respond to pharmacologic treatment. Preoperative assessment of bone vascularity by radionuclide bone blood flow can help direct perioperative medical therapy and prevent massive bleeding.

Extradural ossification of the ligamentum flavum and epidural fat can result in compression of the spinal cord or nerve roots and may require surgical decompression. Myelopathy and cauda equina syndrome can occur without evidence of compression on neuroimaging and can respond dramatically to medical therapy (calcitonin or bisphosphonates), suggesting that ischemia due to a vascular steal phenomenon is responsible.

Serum alkaline phosphatase concentrations and urine hydroxyproline are usually increased in patients with neurologic complications, but alkaline phosphatase levels are normal in one-third of those with spinal stenosis. Plain radiographs and radionuclide scans should be obtained to localize disease activity and identify pathologic fractures. Cranial CT or brain MRI and CT myelography or MRI of the spine are necessary to demonstrate compression of neural structures and to exclude other causes of symptoms (Fig. 22-4). Sarcomatous transformation is best assessed with MRI. Patients with neurologic complications should have serum alkaline phosphatase and urinary hydroxyproline level determinations every 6 months. Clinical monitoring of neurologic function in symptomatic patients and repeat radiographs of the skull and weight-bearing long bones are recommended every 6 to 12 months in those with osteolytic lesions.

Medical and surgical management of neurologic complications depends on location, basis, and clinical course. Asymptomatic disease that affects the skull or spine should be treated with bisphosphonates. Patients with neurologic compromise respond to etidronate and intravenous pamidronate. Calcitonin is no longer recommended as the bisphosphonates are

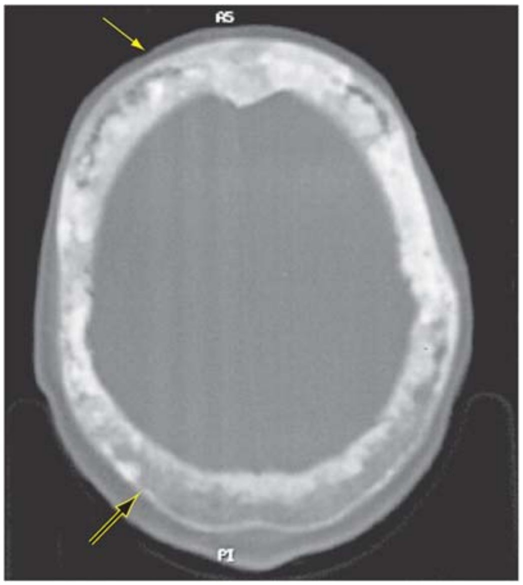

FIGURE 22-4 ■ Paget disease of bone. Axial CT scan of the head with bone windows. The closed arrow shows thickened osteosclerotic bone anteriorly. The open arrow shows thickened hypodense osteolytic bone posteriorly.

more effective with fewer treatment failures.[8] Rapidly progressive neurologic deterioration should be treated with intravenous bisphosphonates before surgery to minimize intraoperative bone hemorrhage.

Obstructive hydrocephalus usually requires the placement of a ventricular shunt. Hydrocephalic dementia with memory loss, gait disturbance, and urinary incontinence may improve with shunting and bisphosphonate therapy.

Bisphosphonate treatment probably results in stabilization of hearing loss. Trigeminal neuralgia and hemifacial spasm are treated with carbamazepine. Hemifacial spasm may also respond to alendronate or botulinum toxin injection. Facial nerve paresis sometimes responds to surgical decompression, and there are older reports of benefit with suboccipital craniectomy and upper cervical laminectomy for patients with lower cranial neuropathies.

Surgical treatment of spinal disease is difficult because involvement is usually at multiple levels, highly vascular bone leads to perioperative bleeding, and patients are typically in an older age group. Some degree of benefit may occur but there is a significant reoperation and mortality rate. Relapses may occur after either bisphosphonate treatment or surgical treatment, and benefit may then follow by repeating or changing therapy.

Inclusion-Body Myopathy, Paget Disease, and Frontotemporal Dementia

Inclusion-body myopathy, Paget disease of bone, and frontotemporal dementia (IBMPFD) is a rare autosomal-dominant disorder caused by missense mutations in the valosin-containing protein (*VCP*) gene.[10] There is variable penetrance of weakness (90%), osteolytic bone lesions (51%), and frontotemporal dementia (32%). The onset of the disorder is in the third and fourth decades, and over half of patients present with weakness. Clinical patterns described include: (1) proximal lower extremity weakness; (2) scapulohumeral weakness with scapular winging; (3) axial weakness with head drop and lumbar lordosis; (4) distal weakness; or (5) a mixture of these patterns. Facial or tongue weakness can occur. The weakness is slowly progressive and is often asymmetric. Other neurologic features include sensorineural hearing loss and sensorimotor axonal neuropathy. A disorder resembling amyotrophic lateral sclerosis in some respects, with upper motor neuron findings, parkinsonism, and myotonia, is described in some families.[10] Patients die of respiratory insufficiency, cardiac failure, or complications from end-stage dementia in the fourth to sixth decades.

Laboratory findings include a serum creatine kinase level that is normal or mildly elevated. Total serum alkaline phosphatase may be elevated if pagetic involvement of bone is present. Standard motor and sensory nerve conduction studies are normal, but EMG shows myopathic units and, sometimes, abnormal spontaneous activity. Patients with an amyotrophic lateral sclerosis-like phenotype may have neurogenic changes by EMG. Neuropsychologic testing is helpful to assess for dementia.

Muscle biopsy shows variation in fiber size and endomysial fibrosis. Subsarcolemmal or sarcoplasmic rimmed vacuoles are present in 40 percent of patients. Electron microscopy shows ubiquitin-positive and tubulofilamentous inclusions similar to sporadic inclusion-body myopathy. A common finding is VCP and TAR DNA-binding protein 43 (TDP-43) inclusions that can co-localize with ubiquitin-positive inclusions. CNS pathology includes atrophy and neuronal loss in the frontal and temporal lobes with ubiquitin-positive inclusions that are positive for TDP-43 in 55 percent of patients.[10]

VCP DNA sequencing is available to make the diagnosis but, interestingly, *VCP* mutations are also described in 2 percent of patients with familial amyotrophic lateral sclerosis. The exact pathogenesis of *VCP* mutations is not completely understood but may relate to impairment of protein degradation. There is no current treatment for the myopathy and dementia in these patients other than supportive measures. Symptomatic Paget disease is treated with bisphosphonates. Other genetic mutations can cause multisystem proteinopathies with Paget disease of bone as one feature. These include *HNRNPA2B1*, *HNRNPA1*, and *SQSTM1*.

VERTEBRAL OSTEOMYELITIS

Infection of the spine by a variety of pathogenic organisms is primarily a disease of older adults; men are affected twice as commonly as women, and recent observations suggest an increasing incidence. Bacteria most commonly reach the spine by hematogenous spread from a distant source, but may also originate from a focus of contiguous infection or be introduced by direct penetrating trauma, surgery, epidural injections, or, rarely, lumbar puncture. Risk factors include degenerative spine disease, intravenous drug use, endocarditis, diabetes, corticosteroid use, immunocompromise, and prior spine surgery.

The lumbar spine is most commonly affected, followed by the cervical spine. With hematogenous spread, septic emboli lodge in the metaphyseal subchondral area of the vertebra, often causing bone infarction. Infection within the vertebral body then tends to spread sequentially to involve the adjacent (avascular) intervertebral disc followed by the next adjacent vertebra (spondylodiscitis). This propensity to traverse disc spaces distinguishes osteomyelitis clinically and radiographically from neoplasia, which tends to remain confined. Abscesses may form when infection extends beyond the cortex of the vertebra. An epidural abscess may cause both radicular injury and spinal cord compression. Extraspinal abscesses may track to a variety of sites (e.g., paraspinal, retroperitoneal, psoas muscle). Chronic osteomyelitis is characterized pathologically by necrosis of bone, a predominantly mononuclear infiltrate, fibrosis, and a paucity of organisms. A sinus tract may develop occasionally between the affected bone and skin.

Osteomyelitis resulting from blood-borne bacterial seeding is almost always the result of infection by a single organism. Diabetes and chronic alcoholism are common risk factors. More than half are due to *Staphylococcus aureus* (meticillin-susceptible isolates account for the majority) and are often associated with vascular catheters and other invasive medical procedures. Causative organisms also include *Escherichia coli* and other enteric gram-negative bacteria, *Brucella*, and fungi (e.g., *Candida*). *Pseudomonas* and staphylococcal infections are associated with intravenous drug use. Streptococci and enterococci are frequently associated with endocarditis. Tuberculous infection is addressed elsewhere in this chapter. Polymicrobial ("mixed") cultures are associated with trauma and spread of contiguous infection.

Back pain, often with local tenderness, is the most frequent presenting feature. Pain is often not relieved by rest; it persists at night and may radiate to the abdomen, pelvis, or lower limbs. The spine may be held rigidly, with paraspinal muscle spasm. In many patients, back pain is preceded by a subacute prodrome of constitutional symptoms—fever, fatigue, lethargy, anorexia—for several weeks. By the time of initial presentation, however, the patient may be afebrile with few other signs of systemic infection. Neurologic deficit occurs in only one-half of the patients and constitutes the major complication. Vertebral collapse may cause spinal cord compression. Encroachment on sensory and motor roots gives rise to pain and segmental sensorimotor loss. Cauda equina syndrome may result from compression of multiple lumbosacral roots. Epidural abscess formation with compression of the spinal cord may develop acutely or subacutely over several weeks and requires immediate surgical decompression.

A high index of clinical suspicion is required for the timely diagnosis of osteomyelitis. Identification is crucial, because effective antibiotic therapy may prevent necrosis of bone and permanent skeletal abnormality. Plain radiography is frequently normal in the first 2 to 4 weeks since lytic lesions are not apparent until significant bone loss has occurred. By contrast, MRI abnormalities (Fig. 22-5)—commonly hypodensities within the vertebral body and contrast enhancement of the body and disc—can be seen in early disease, representing edema; other findings include spondylodiscitis, erosion of bone, and intra- and extravertebral collections. Radionuclide scans are highly sensitive but the findings are nonspecific; this technique is particularly useful when MRI is contraindicated.

Blood cultures are positive in around 30 percent of cases. Material from the focus of infection may be obtained by needle aspiration or open biopsy, and is generally needed to confirm the diagnosis. Biopsy may be avoided if blood cultures are positive for an appropriate organism, and there is confidence

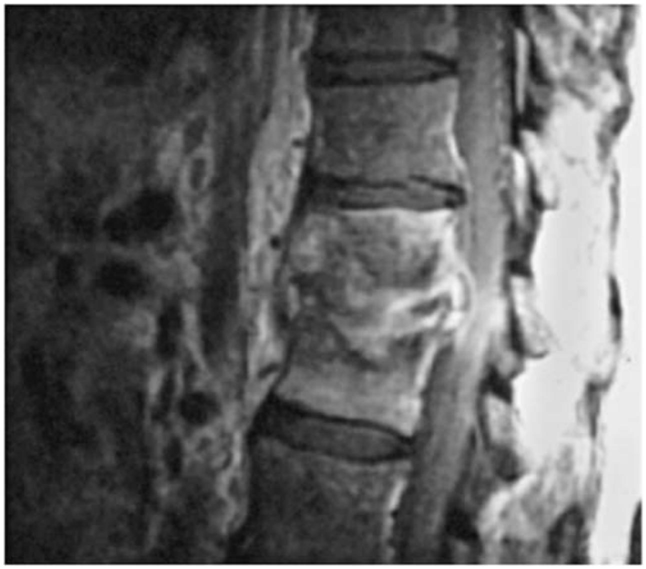

FIGURE 22-5 ■ Osteomyelitis. Sagittal T1-weighted MRI of the lower thoracic spine, with contrast. A septic focus is seen to involve the intervertebral disc and the two adjacent vertebral bodies. An epidural abscess compresses the thecal sac.

regarding the diagnosis. Specimens for microbiologic culture and antibiotic sensitivity should be obtained before the institution of antibiotic therapy, although one study found that antibiotics administered prior to biopsy did not reduce culture yield.[11] The concurrent presence of endocarditis should always be considered, particularly in the setting of underlying valvular disease and gram-positive cultures. A second biopsy may be needed if the first is negative. Brucellosis and tuberculosis serology may be helpful.

High-dose intravenous antibiotics are used for treatment although there are no randomized, controlled trials to evaluate specific regimens or duration of therapy. Choice of agent is determined by tissue or blood culture and sensitivity testing. Treatment for 6 to 12 weeks with antibiotics may be needed. Empiric treatment (usually a penicillinase-resistant penicillin or vancomycin, plus a third-generation cephalosporin) may be necessary before microbiology results return or when cultures are negative. Intravenous antibiotics should be continued for an extended period of weeks to months before switching to an oral preparation once a favorable response has been achieved. Close monitoring in the first few weeks is essential to identify complications such as cord compression and abscess formation. If there is no improvement clinically (pain, fever), or settling of the erythrocyte sedimentation rate and C-reactive protein level within 3 to 4 weeks, biopsy may need to be repeated. Imaging abnormalities tend to persist despite clinical measures of improvement and are not necessary to follow routinely. In contrast, the erythrocyte sedimentation rate and C-reactive protein level are frequently elevated and may be useful to follow weekly to gauge response to therapy. Bed rest with external immobilization with a back brace is generally enforced until back pain has receded. With appropriate antibiotic therapy, recovery is the rule; surgery is required in 10 to 20 percent of cases, usually for drainage of large abscesses, decompression in cases of progressive neurologic deficit, particularly cord compression, fixation for spinal instability, and debridement in severe, unresponsive infection. Prognosis is worse in older patients and when there is a delay in diagnosis. A systematic review found an overall mortality of 6 percent, with residual deficit seen in 32 percent of patients.[12] Osteomyelitis resulting from trauma or contiguous infection requires broad-spectrum antibiotic therapy due to its polymicrobial nature and, frequently, surgical debridement. The management of chronic osteomyelitis is difficult and controversial, usually involving complete surgical removal of the nidus of infection along with long-term antibiotic therapy.

Tuberculous Osteomyelitis

First reported in detail by Sir Percivall Pott in the late eighteenth century, tuberculous involvement of bone and joint tissue accounts for 10 to 35 percent of cases of extrapulmonary tuberculosis worldwide, with the spine (Pott disease) being the most common site of skeletal involvement. Immigrants from endemic areas to developed countries have higher rates of extrapulmonary tuberculosis. Tuberculous infection of the spine may occur by hematogenous seeding at the time of primary infection (typically children in endemic areas) or as a result of reactivation of a focus of latent infection with hematogenous or lymphatic spread to the spine, frequently years after the initial pulmonary infection (typically adults in nonendemic areas). Usually, a vertebral body in the lower thoracic or upper lumbar spine is affected, followed by spread to adjacent vertebrae. Involvement of the intervening disc occurs later than in bacterial osteomyelitis and may give rise to a radiologic appearance of relative disc-sparing. Destruction of cancellous bone renders the involved vertebral body liable to compression fractures and vertebral body collapse. In advanced cases, both kyphosis and scoliosis can produce a striking gibbus deformity which may be associated with (thoracic) myelopathy. Paravertebral collections may form at various sites including within the psoas muscle. Occasionally, contiguous spread is seen from a primary focus in the lung apex to the atlanto-axial joint.

Back pain is common and patients may adopt a stiff-backed posture, walking with careful, short steps to avoid jarring the spine. Constitutional symptoms (lethargy, night sweats, weight loss) and systemic signs (anemia, low-grade fever) are frequent but may not be prominent. Neurologic deficits are present in fewer than one-half of patients. The possibility of tuberculous infection of the spine is usually an obvious consideration in patients with known pulmonary tuberculosis (particularly when treatment was incomplete), or in immunosuppressed patients. In the majority of patients, however, there is no history of tuberculosis, and a high index of clinical suspicion and appropriate (radiologic) investigations are needed for recognition; in many series, diagnosis was delayed for 12 to 18 months after presentation.

There may be few clues to the diagnosis on routine tests: erythrocyte sedimentation rate and C-reactive protein may not be elevated, and the peripheral white count may be normal or elevated only slightly. Chest radiography is normal in half the cases, and sputum is usually negative for acid-fast bacilli. CT or MRI may show involvement of the anterior aspect of a vertebral body, later with involvement of several contiguous vertebral bodies with heterogeneous enhancement and the presence of epidural and subdural abscesses. The intervening discs may not show involvement, unlike the case with pyogenic infections. The differential diagnosis may include degenerative disease, compression fractures, bacterial and fungal osteomyelitis, and metastatic disease.

Attempts to confirm the tuberculous nature of such lesions usually begin with a purified protein derivative (PPD) skin test, which has poor sensitivity. Biopsy (needle aspiration or open biopsy) demonstrates the characteristic caseating granulomatous histology with Langhans giant cells and acid-fast bacilli; culture may be positive.

Treatment is with prolonged antituberculous drugs similar to the approach used for pulmonary tuberculosis. The duration of therapy is unclear and is judged according to clinical response. In general, 6 to 9 months of initial treatment with a regimen of first-line drugs including rifampin is sufficient in uncomplicated disease; a longer 9- to 12-month course with or without surgical debridement may be needed in advanced disease or where the drug regimen does not include rifampin. Drug-resistant infection may require prolonged therapy for 18 to 24 months. In patients infected with human immunodeficiency virus, spinal tuberculosis may worsen following institution of antiretroviral therapy as a result of immune reconstitution inflammatory syndrome. Response to treatment may take weeks to months by clinical and laboratory measures, but radiologic changes tend to persist, suggesting that imaging need not be repeated in patients who are improving. Surgical debridement and stabilization of the spine is sometimes required in addition to drug therapy for those patients with spinal instability or severe disease, but should not be performed routinely. Spinal cord compression is a medical emergency necessitating immediate surgical decompression.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis is an HLA-B27-associated chronic inflammatory disease of joints with predilection for the sacroiliac joints and spine and with ossification of associated ligaments (enthesopathy). HLA-B27 is present in 74 to 89 percent of patients with the disorder.[13] Clinical manifestations typically begin in late adolescence or early adulthood. The most common symptoms are pain and stiffness of the low back and pelvis. Pain can be severe and is often referred along the iliac crest to the greater trochanteric region or down the dorsal thigh. It sometimes alternates from side to side and may be accentuated by cough, sneeze, or a twisting motion of the back. Features that help to differentiate it from mechanical low back pain include the onset of back discomfort before the age of 45, an insidious onset, persistence for at least 3 months, associated morning stiffness, improvement with exercise, and failure to improve with rest. Within a few months of onset, as symptoms become persistent, the pain becomes bilateral and prominent at night, and is relieved by getting up and walking around. Pain in the chest occurs in 40 percent.[13]

The findings on physical examination include flattening of the lumbar spine and loss of the lumbar

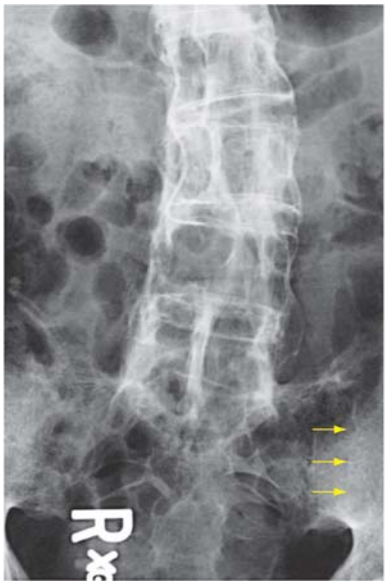

FIGURE 22-6 ■ Ankylosing spondylitis. Plain radiograph of lumbosacral spine. The characteristic "bamboo spine" with fusion of the intervertebral ligaments is evident. The arrows show fusion of the sacroiliac joint.

lordosis. There is limited motion of the axial skeleton, especially with hyperextension and lateral bending. Percussion over the sacroiliac joints elicits pain. Radiographs or MRI of the sacroiliac joints are used to make the diagnosis in conjunction with the clinical features and laboratory investigations, including C-reactive protein, erythrocyte sedimentation rate, and HLA-B27 (Fig. 22-6).

Therapies for ankylosing spondylitis that have evidence-based beneficial effects include physical therapy, NSAIDs, and tumor necrosis factor alpha (TNF-α) inhibitors. It is unclear whether these therapies alter the course of the illness, particularly the loss of spinal mobility, with the possible exception of the TNF-α inhibitors. Intensive physical therapy and exercise are important to maintain mobility, posture, and range of motion. Braces, splints, and corsets should be avoided. NSAIDs are the first line of therapy for pain and stiffness. For patients who cannot tolerate continuous NSAIDs or who do not have adequate control, TNF-α inhibitors are recommended. Younger age, milder disease, short disease duration, elevated nonspecific markers of inflammation, and HLA-B27 positivity are associated with better response to TNF-α inhibitors. Interleukin-17 inhibitors are a promising new approach to treatment. A detailed description of treatments for ankylosing spondylitis is provided elsewhere.[13]

Neurologic complications are uncommon. They include radiculopathy from foraminal stenosis or inflammation and myelopathy resulting from fracture-dislocation, atlanto-axial subluxation, pseudoarthritis, ossified intraspinal ligaments, or granulation tissue. Cauda equina syndrome is a late complication attributed to arachnoiditis. Sciatic nerve compression can occur secondary to inflammation of the attachment of the piriformis muscle to the sacroiliac joint, mimicking sciatica from root compression (pseudosciatica).

The risk of spine fractures in patients with ankylosing spondylitis is 10 percent. The spine is brittle and thus prone to fracture, and osteoporosis in these patients is another important risk factor. Fracture risk worsens with age and is more common in men. The fracture often goes entirely through the vertebral body and/or calcified disc and ossified ligaments, resulting in increased instability and a high risk of neurologic compromise. The most common fracture location is in the low cervical spine and in the majority of cases results from low-energy trauma. Secondary neurologic compromise can also occur, with deterioration sometimes occurring more than 3 months after the initial fracture. Delayed diagnosis is common, due to physician misdiagnosis or patient delay in seeking care. Sudden neck or back pain in these patients should prompt a CT and possibly an MRI of the spine to search for fracture.

Surgical intervention is complicated but appears to have a greater chance of improvement or stabilization of neurologic function and a lower mortality than nonoperative treatment, although selection bias is a factor.[14] There is a high failure rate for nonoperative treatment. Bracing must be customized and risks impairing pulmonary function. Traction is not recommended. If possible, a combined anterior and posterior surgical approach is recommended for cervical fractures. For craniovertebral junction fractures, posterior segmental stabilization after reduction is the usual approach. For thoracic and lumbar spine fractures, posterior stabilizing surgery is recommended. Surgical complications occur frequently, including postoperative wound infections, deep vein thrombosis, pneumonia, and respiratory insufficiency. Fatal but rare complications of surgery include aortic dissection, aortic pseudoaneurysm, and tracheal rupture.

Spinal stenosis with cord compression is rare. Patients may develop "radicular" pain without neurologic symptoms or signs, and this usually resolves spontaneously. The cervical spine may be involved, resulting in atlanto-axial subluxation in some patients. Atlanto-occipital subluxation with vertebral artery occlusion and brainstem transient ischemic attack or infarction may also occur. Studies of the natural history of ankylosing spondylitis have demonstrated that cerebrovascular disease is a common cause of mortality in patients younger than 60 years of age, often without clear etiology; prophylactic antiplatelet therapy may be indicated.

Cauda equina syndrome occurs in rare patients, predominantly male, on average 32 years after the onset of disease. In most patients, there are no inflammatory markers in the blood. The typical presentation includes insidious onset and progression of bowel and bladder symptoms, sensory loss (often asymmetric) in an L5–S4 distribution, pain radiating into the lower limbs or the rectal area, and minimal weakness in muscles innervated by the L5–S2 segments. Bladder symptoms include decreased awareness of bladder sensation, decreased ability to empty the bladder, hesitancy, decreased force of urinary stream, urgency, and frequency. Radiography of the lumbar spine may show erosions of the lamina. Spinal MRI shows dorsal dural diverticula associated with a widened thecal sac and scalloped erosions of the laminae and spinous processes. Nerve roots appear to deviate toward the diverticula and may be displaced posteriorly; they appear to be adherent to the arachnoid membrane and to each other, suggesting arachnoiditis. There is no associated gadolinium enhancement. Spinal CT typically demonstrates asymmetric, multilevel erosions that selectively involve the pedicles, laminae, and spinous processes of the lumbosacral spine. Infrequently, erosion of the posterior portion of the vertebral body is found, or involvement is unilateral or confined to one level. Myelography is technically difficult and can be complicated by epidural hematoma in patients with ankylosing spondylitis. CSF is normal or shows a slightly elevated protein concentration, although rarely a lymphocytic pleocytosis occurs. EMG shows denervation changes, often asymmetric, in the L2–S1 distribution.

The pathologic findings depend on the timing of surgery or autopsy relative to the onset of neurologic symptoms. Early pathologic findings include inflammation of the spinal ligaments, dura, and arachnoid. Over time, there is fibrosis and chronic arachnoiditis embedding atrophic nerve roots, with small sacral roots splayed and adherent to the dura. A CSF resorption defect has been documented and may contribute to thecal sac enlargement. Compression of the nerve roots by diverticula sometimes occurs. The disease may be patchy, with some roots appearing normal.

NSAIDs result in improvement of back pain in cauda equina syndrome, but without improvement of neurologic deficits. There can be partial improvement with infliximab. Patients may have improvement of neurologic function or halting of progression with either lumboperitoneal shunting or laminectomy, but neurologic deficits persist despite surgical intervention in most patients. The clinical course is slowly progressive, although patients rarely lose the ability to walk. Any patient with longstanding ankylosing spondylitis who develops sphincter dysfunction should receive a careful neurologic assessment.

There is an unclear association between ankylosing spondylitis and multiple sclerosis. There is an increased incidence of autoimmune neurologic disorders including multiple sclerosis and demyelinating neuropathy in rheumatologic patients, including those with ankylosing spondylitis, treated with TNF-α inhibitors. There may be more CNS side effects with etanercept therapy, and peripheral nervous system side effects with infliximab. The incidence of these complications in patients with ankylosing spondylitis treated with TNF-α inhibitors is unknown. It is recommended in these cases that the TNF-α inhibitor be discontinued; some, but not all, patients improve after discontinuation. The use of TNF-α inhibitors in patients with a prior history of multiple sclerosis or a CNS demyelinating disorder is best avoided. Demyelinating neuropathy should be treated with corticosteroids or intravenous immunoglobulin.

Diffuse Idiopathic Skeletal Hyperostosis

Diffuse idiopathic skeletal hyperostosis is a noninflammatory arthropathy with ossification of spinal longitudinal ligaments and entheses resulting in decreased mobility and ankylosis. The etiology is unknown but there is an association with male gender, obesity, adult-onset diabetes mellitus, pulmonary hypertension, and advanced age. Diagnosis is made by the presence of ossification of the anterior longitudinal ligament over four consecutive levels on spine radiographs. The most common areas of involvement are T7 to T11. Common clinical symptoms are pain and stiffness in the spine. Serious complications from cervical spine involvement include dysphagia, sleep apnea, difficult endotracheal intubation, and spinal canal stenosis with myelopathy.

There is an increased incidence of traumatic vertebral fracture in these patients, and they are more likely to have multiple fractures. A unique feature is fracture through the vertebral body. The cervical spine is the most common site involved. Low-energy impact commonly precedes fracture but high-energy impact is recognized in about a quarter of patients. Hyperextension is the most frequent cause. There is delay in diagnosis of the fracture in more than half of patients and almost one-half have a neurologic deficit on presentation. Secondary neurologic deterioration may occur and is sometimes due to inadequate immobilization, inconsiderate transfers, or the application of a hard collar with a pre-existing kyphotic deformity. About half of these patients are treated with surgical posterior fixation, and the rest are managed conservatively, often with a collar or bracing for thoracic fractures. Neurologic improvement is unlikely regardless of treatment and there is substantial morbidity and mortality in both operated and unoperated cases. Pneumonia, respiratory failure, and pseudoarthosis are described most frequently.

RELAPSING POLYCHONDRITIS

Relapsing polychondritis is an uncommon, immune-mediated multisystem disorder characterized by recurrent episodes of inflammation and eventual destruction of cartilaginous tissues. The prevalence of the disorder is 3.5 per 1 million persons, with an age range from 16 to 84 years, with peak onset in the fifth decade.[15] There is an equal prevalence in men and women, and it has been described in all races. It can affect all types of cartilage, including the ears and nose (most commonly), peripheral joints, fibrocartilage at axial sites, and the tracheobronchial tree. The eye, heart, blood vessels, and inner ear are rich in proteoglycans and can also be affected. There is a genetic association with HLA-DR4 and negative association with HLA-DR6. More than 30 percent of patients with relapsing polychondritis have an associated hematologic or rheumatologic disorder (especially a vasculitis associated with antineutrophil cytoplasmic antibodies). Antibodies to types II, IX, and XI collagen can be present, and immune-complex deposition is found in cartilage.

The clinical presentation involves the acute or subacute onset of ear pain, tenderness and swelling of the external auditory meatus, erythema, and a clear serous discharge from the ear (Fig. 22-7). Ear involvement is often the initial presenting symptom and ultimately occurs in almost all patients. The noncartilaginous lobule is spared. Repeated bouts of inflammation result in a floppy ear. Nasal pain, hoarseness, and difficulty in talking are also common. Nasal crusting, rhinorrhea, and epistaxis can occur, and repeated inflammation of the nasal cartilage results in a saddle nose deformity. Systemic symptoms include fever, lethargy, and weight loss. The course is typically relapsing, but over the course of the illness, progressive disability occurs in most patients. Inflammation of the trachea and larynx occurs in 50 percent of patients and may be fatal. A detailed description of the cardiovascular, joint, respiratory, and dermatologic complications is provided elsewhere.[15]

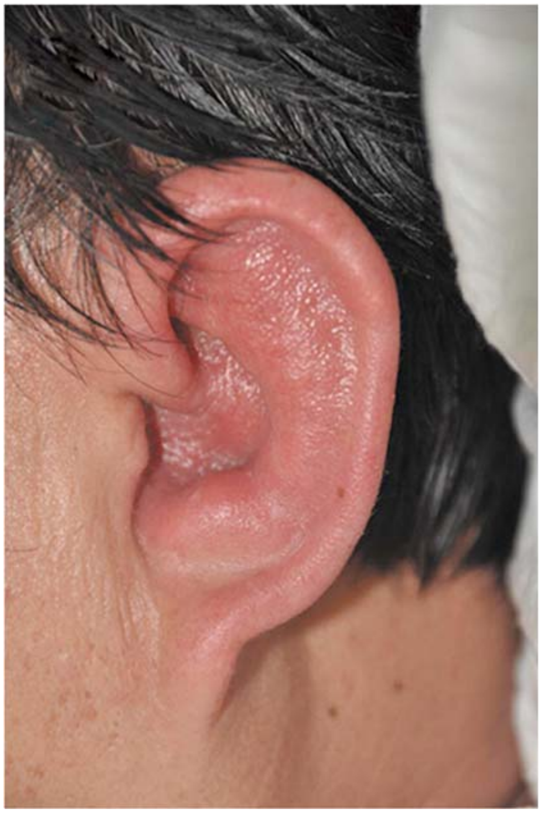

FIGURE 22-7 ■ Relapsing polychondritis, illustrating marked auricular swelling and redness. (From Wang ZJ, Pu CQ, Wang ZJ, et al: Meningoencephalitis or meningitis in relapsing polychondritis: four case reports and a literature review. J Clin Neurosci 18:1608, 2011, with permission.)

Vertigo, conductive or sensorineural hearing loss, and tinnitus are common and can be the presenting symptom. The sensorineural hearing loss is attributed to vasculitis of the vestibular or cochlear branch of the internal auditory artery. The abrupt onset of hearing loss, sometimes accompanied by vertigo, nausea, vomiting, and imbalance, can mimic a posterior circulation stroke. Ocular involvement occurs in 65 percent of patients including recurrent conjunctivitis, episcleritis, scleritis, iritis, or keratoconjuctivitis sicca. Rarely, chorioretinitis, retinal vasculitis, exophthalmos due to orbital pseudotumor, uveitis, and optic neuritis are seen. Extraocular palsies occur either due to direct extension of pseudotumor-like inflammation of the orbit or from vasculitic ischemia to cranial nerves III, VI, or IV.

Vasculitis occurs in up to half of patients with relapsing polychondritis and affects the skin, internal organs, or CNS. It can affect the large arteries, resembling Takayasu arteritis, or small- to medium-sized vessels. The prognosis in patients with systemic vasculitis is poor, with a 5-year survival rate of 45 percent.

Neurologic involvement is infrequent but may be the presenting feature. It may manifest with cranial neuropathies, cerebral vasculitis, mononeuritis multiplex, sensorimotor distal symmetric neuropathy, aseptic meningitis, meningoencephalitis with limbic encephalopathy, rhombencephalitis, myelitis, acute spinal cord infarction due to aortic disease, or thromboembolic strokes secondary to vasculitis, sometimes with associated anticardiolipin antibodies. Cerebral aneurysms occur in rare instances.

Cranial nerve abnormalities are the most frequent, with involvement of II, VI, VII, and VIII being most common. Involvement of III, IV, and XII has also been described. Vasculitic infarction is the presumed etiology. CNS involvement can be due to vasculitis or meningoencephalitis; patients present with an acute headache accompanied by encephalopathy, personality change, hallucinations, seizures, and focal or multifocal deficits such as hemiparesis, ataxia, or the clinical features of a lateral medullary syndrome. An acute limbic encephalitis can present with fever, delirium, visual and auditory hallucinations, agitation, disinhibition, cognitive decline, and seizures. There may be an association with antiglutamate receptor ε2 antibodies. CSF may show a pleocytosis and elevated protein concentration. Parkinsonism, apathy, psychosis, and dementia may also develop. Papilledema or meningeal signs can occur. Aseptic meningitis presents with headache, meningeal signs, and fever; in these cases, CSF results most often show a lymphocytic pleocytosis, but a polymorphonuclear leukocyte predominance sometimes occurs. Total protein level can be elevated markedly and there are cases with a decreased CSF glucose mimicking infection. Oligoclonal bands are sometimes present. MRI may show patchy thickening of the dura mater with gadolinium enhancement. With meningoencephalitis, T2 and FLAIR hyperintensity and enhancement are also seen in the gray and white matter in a patchy distribution. Recurrent encephalitis can result in atrophy of affected areas.

With CNS vasculitis, the erythrocyte sedimentation rate is usually elevated (> 100 mm/hour), and mild systemic leukocytosis may be present. The CSF is normal or shows a pleocytosis. The electroencephalogram can be normal, slow, or show focal areas of epileptiform activity. Cranial CT often shows cerebral and cerebellar atrophy or focal areas of hypodensity, but it can be normal. MRI is suggestive of cerebral vasculitis, with increased T2 signal in the periventricular white matter and centrum semiovale, focal lesions in the gray matter, and wedge-shaped cortical infarcts. Focal occlusion of vessels can be seen on MR angiography. In cases of limbic encephalitis, the MRI shows increased T2 signal in one or both medial temporal lobes. A clue to the diagnosis of relapsing polychondritis in some patients with neurologic presentations is increased signal on diffusion-weighted imaging of the external ears (Fig. 22-8). Brain biopsy in these cases shows marked gliosis, perivascular cuffing, and destruction of the vascular well.

The diagnosis of relapsing polychondritis is based on clinical criteria (Table 22-4), supportive laboratory parameters, imaging, and biopsy of involved cartilaginous tissues, including the ear. Evaluation of organ involvement on physical examination is critical, including the ear, nose, and throat. Nonspecific laboratory findings include an elevated erythrocyte sedimentation rate and C-reactive protein level, anemia, leukocytosis, and thrombocytosis. Esoinophilia may be present. Serum creatinine and urinalysis should be checked to assess for renal involvement. A serologic screen for associated rheumatologic disorders should occur. Type II collagen antibodies may be present. The airway and lungs should be evaluated by radiography, pulmonary function tests, and high-resolution CT scans, specifically dynamic expiratory CT. Echocardiogram to evaluate the heart valves is also recommended. PET-CT is a newer technique to determine the distribution of lesions in relapsing polychondritis and help target tissue biopsy. MRI of the joints and ear can also be helpful for early diagnosis. Early pathology of affected cartilaginous tissue shows a pleomorphic inflammatory infiltrate.

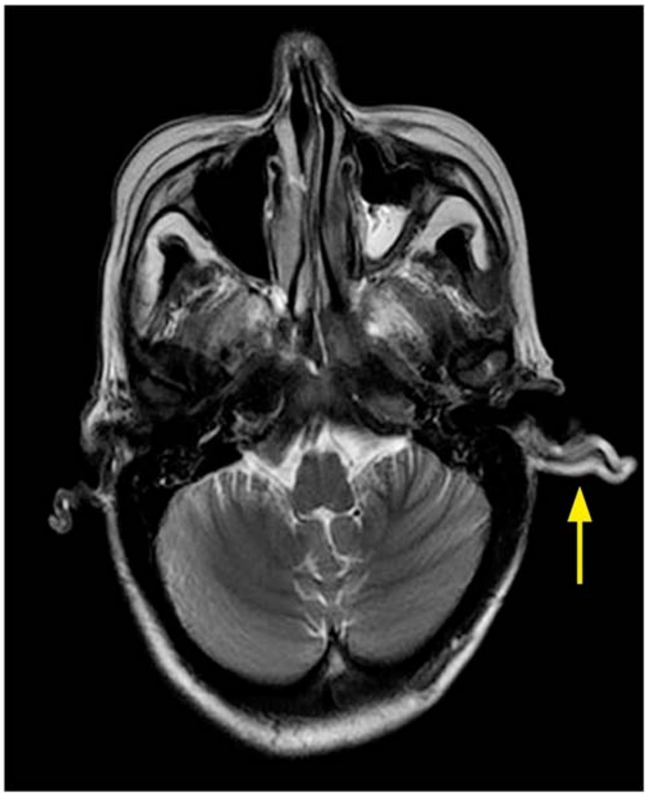

FIGURE 22-8 ■ Relapsing polychondritis. T2-weighted MRI showing abnormal signal in the left auricle. (From Wang ZJ, Pu CQ, Wang ZJ, et al: Meningoencephalitis or meningitis in relapsing polychondritis: four case reports and a literature review. J Clin Neurosci 18:1608, 2011, with permission.)

TABLE 22-4 ■ **Diagnostic Criteria for Relapsing Polychondritis***

Bilateral auricular chondritis
Nonerosive seronegative inflammatory arthritis
Nasal chondritis
Ocular inflammation
Respiratory tract chondritis
Audiovestibular damage

*A minimum of three criteria must be met to establish the diagnosis.

T lymphocytes are mainly CD4-positive. There is inconstant deposition of Ig and C3 at the junction between the perichondrium and cartilage. With time, inflammatory infiltrates invade the cartilage and there is progressive destruction of the cartilage with replacement by collagen.

The differential diagnosis includes Wegener granulomatosis. Distinguishing clinical features include involvement of the mucosa and lung parenchyma and the presence of positive cytoplasmic antineutrophil cytoplasmic antibodies, which are not seen in uncomplicated relapsing polychondritis.

Treatment is empiric as there are no standardized therapeutic guidelines. Mild inflammation of joints, ear, or nose can be managed with NSAIDs, dapsone, or colchicine. If there is significant laryngotracheal, bronchial, cardiovascular, renal, or neurologic involvement, a more aggressive course is recommended. Rapid response is obtained with high-dose oral or intravenous corticosteroids. Relapses occur if corticosteroids are reduced too rapidly. Corticosteroid-sparing agents may be necessary, including cyclophosphamide, azathioprine, cyclosporine, and methotrexate. TNF-α inhibitors are of particular interest since there is a massive expression of TNF-α in affected cartilaginous tissue in patients with relapsing polychondritis. There are mixed results for treatment with biologic agents, with best outcomes with infliximab, followed by etanercept and rituximab. Similarly there are limited data concerning the efficacy of adalimumab, toclizumab, abatacept, leflunomide, mycophenylate mofetil, and intravenous immunoglobulin in refractory cases or when there is loss of efficacy of first-line agents. Certolizumab and rituximab are not recommended. Elevated serum IL-6 levels may predict response to tocilizumab.

Treatment of CNS vasculitis, limbic encephalitis, meningoencephalitis, and aseptic meningitis includes high-dose corticosteroids, often with additional corticosteroid-sparing agents during the course of the illness. Limbic encephalitis can respond dramatically to infliximab. Aseptic meningitis in relapsing polychondritis responds to corticosteroids in most cases.

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SECTION

7

The Ears, Eyes, and Related Systems

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CHAPTER

23

Otoneurologic Manifestations of Otologic and Systemic Disease

JOSEPH M. FURMAN ■ ANDREW A. McCALL

NEUROLOGIC MANIFESTATIONS OF OTOLOGIC DISEASE
- Complications of Middle Ear Pathology
- Labyrinthine Disorders
- Eighth Nerve Lesions
- Cerebellopontine Angle Disorders
- Superior Semicircular Canal Dehiscence Syndrome
- Central Vestibular Disorders
- Central Auditory Processing Disorder

OTONEUROLOGIC MANIFESTATIONS OF SYSTEMIC DISEASE
- Infection
- Immune-Mediated and Connective Tissue Disease
- Neurocutaneous Syndromes
- Metabolic and Endocrine Disorders
- Diseases of Bone
- Drug-Induced Disorders
- Environmental Disorders
- Nutritional Disease
- Neoplastic Disease

NEURO-OTOLOGIC MANIFESTATIONS OF AGING
- Dysequilibrium of Aging
- Presbycusis

NEUROLOGIC MANIFESTATIONS OF OTOLOGIC DISEASE

Complications of Middle Ear Pathology

Intracranial complications occur in 0.25 to 0.5 percent of all cases of otitis media. The mortality rate of intracranial complications has decreased dramatically over the last century, from approximately 90 percent in the preantibiotic era to 10 percent now. However, significant morbidity still exists despite this improvement in survival. Diagnosis of an intracranial complication of otitis media relies heavily on an accurate history and a high index of suspicion. Important elements include determining whether the patient has acute or chronic otitis media, a prior history of otologic disease or surgery, a history of head trauma or temporal bone fracture, previous antibiotic treatment, and symptoms suggesting intracranial involvement such as headache, lethargy, visual changes, fever, and nausea or vomiting.[1]

The differential diagnosis for a patient with otitis media and symptoms and signs of intracranial involvement is long, and potential complications are numerous, including extradural abscesses or granulation tissue, dural venous sinus thrombosis, petrous apicitis (Gradenigo syndrome; Fig. 23-1), intraparenchymal brain abscesses, subdural abscesses, otitic hydrocephalus, and meningitis (most commonly purulent).[1]

The microbiology of the intracranial complications of otitis media varies with the duration of otitis as well as the type of complication. Complications of acute otitis media usually are secondary to *Streptococcus pneumoniae* or *Haemophilus influenzae*. Chronic otitis media frequently leads to complications with gram-negative bacteria, such as *Pseudomonas aeruginosa*, or anaerobes.[1] The most common organisms implicated in otitic meningitis include *S. pneumoniae*, *H. influenzae*, *Proteus* species, *P. aeruginosa*, and *Staphylococcus aureus*. Brain abscesses are typically polymicrobial.

If an intracranial complication is suspected on the basis of the history or physical findings, further evaluation should include computerized tomography (CT) of the temporal bones to evaluate for bony erosion, congenital malformation, or fracture; contrast-enhanced magnetic resonance imaging (MRI) or CT of the head to evaluate for enhancement of the meninges, dural sinus thrombosis (Fig. 23-2), or brain

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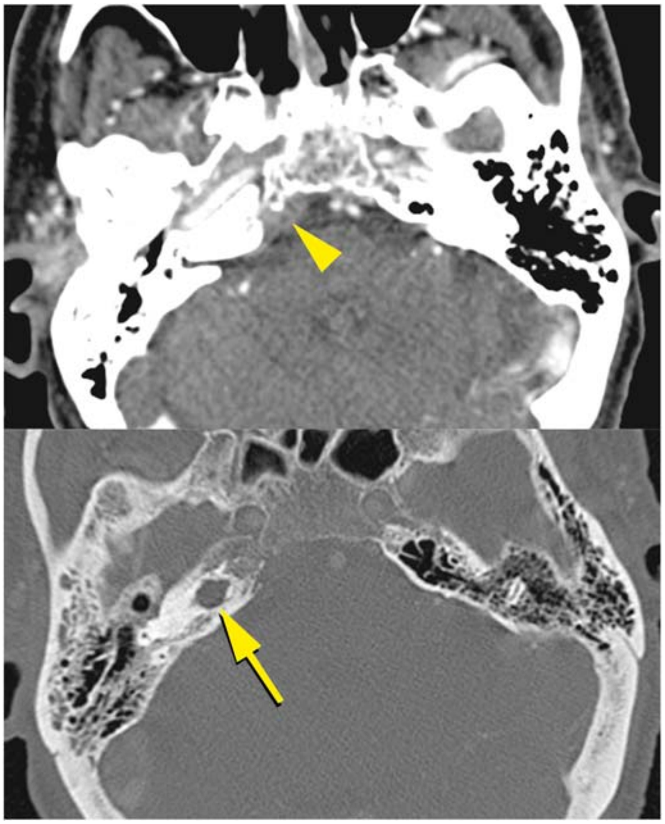


FIGURE 23-1 ■ Computed tomography scan showing right petrous apicitis. *Upper scan*: Soft tissue windowing demonstrating enhancement at the tip of the petrous apex affecting Dorello canal (*arrow head*). *Lower scan*: Bone windowing demonstrating a lytic cell in the petrous apex with loss of septation (*arrow*). (Courtesy of Hugh D. Curtin, MD, Massachusetts Eye and Ear Infirmary, Boston.)

abscess; and a lumbar puncture if no mass effect is visualized on imaging.[1] The cerebrospinal fluid (CSF) will typically show increased protein and decreased glucose concentrations along with organisms on Gram stain in bacterial meningitis; those patients given antibiotics in the days or weeks preceding the spinal tap may have more normal-appearing CSF chemistries and a negative Gram stain, but should be treated with antibiotics until cultures are negative, given the possibility of a partially treated bacterial meningitis. In otitic hydrocephalus, the opening pressure will be increased, but the other studies will be normal.

Treatment of the intracranial complications of otitis media includes medical stabilization and usually requires inpatient admission. Broad-spectrum intravenous antibiotics should be initiated empirically. Surgical consultation with an otolaryngologist or neurosurgeon should be obtained to assess for drainage of the primary source and address intracranial complications that warrant such procedures (such as intracranial abscess). Complications due to acute otitis media may be treated with a second- or third-generation cephalosporin to target the usual three pathogens: *H. influenzae*, *Moraxella catarrhalis*, and *S. pneumoniae*. Gram-negative and anaerobic coverage should be added for complications of chronic otitis media. Corticosteroids such as dexamethasone should be administered concurrently with intravenous antibiotics for otogenic meningitis in order to reduce the chance of sensorineural hearing loss and, in meningitis caused by *S. pneumoniae*, to reduce mortality.[1]

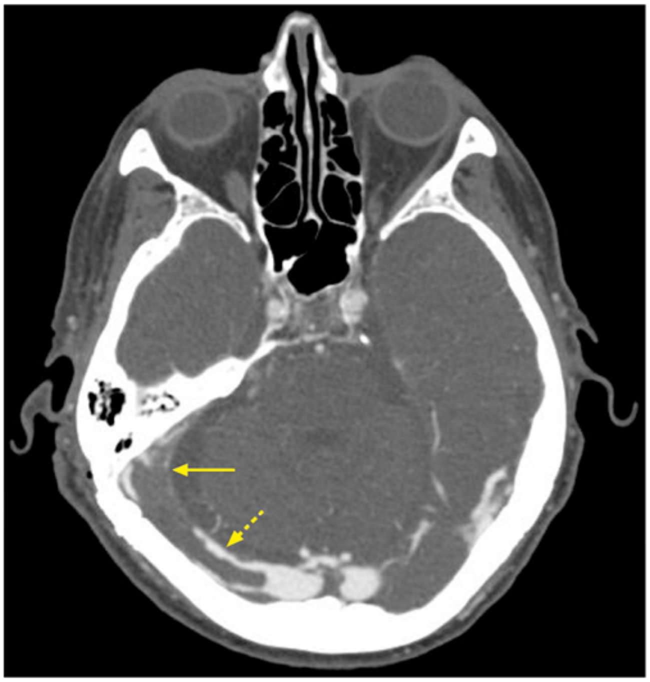


FIGURE 23-2 ■ Sigmoid sinus thrombosis. CT venography performed after retromastoid craniectomy reveals a filling defect in the right transverse (*dashed arrow*) and sigmoid (*solid arrow*) sinuses, representing subocclusive thrombus. (Courtesy of Barton F. Branstetter, MD, University of Pittsburgh.)

Labyrinthine Disorders

Meniere disease and benign paroxysmal positional vertigo are two of the most common labyrinthine disorders that cause vertigo and dysequilibrium. The pathologic correlate of Meniere disease is endolymphatic hydrops, which is usually idiopathic but may occur following inner ear trauma or infection. Patients with Meniere disease typically experience episodes of unilateral tinnitus, unilateral hearing loss, unilateral ear fullness, and vertigo lasting for minutes to hours. They do not typically experience neurologic symptoms that cannot be attributable directly to the inner ear.[2] However, some patients experience visual changes, especially blurred vision, during attacks of Meniere disease, and headaches may occur. Other patients become anxious during attacks and may experience numbness and paresthesias. The first attack of Meniere disease often prompts an evaluation in an emergency department, leading to brain imaging to exclude cerebellar hemorrhage or infarction. First-line treatment of Meniere disease consists of sodium restriction and a diuretic, typically a combination of hydrochlorothiazide and triamterene. Nonablative procedures, such as intratympanic steroid infusion, and ablative procedures, such as intratympanic gentamicin or labyrinthectomy, are options for patients who do not respond to conservative management.[3]

Benign paroxysmal positional vertigo is caused by free-floating otolithic debris in the posterior semicircular canal. As with Meniere disease, benign paroxysmal positional vertigo may follow inner ear trauma or infections but usually is idiopathic. Patients typically have positionally induced vertigo when rolling over in bed or looking up.[4] The vertigo typically lasts for less than 1 minute but more generalized symptoms of dizziness and dysequilibrium may persist for several hours. Neurologic symptoms other than vertigo and transitory visual difficulties are generally absent, although patients may have difficulty in walking due to their vertigo. On physical examination, the findings on Dix–Hallpike maneuvers, illustrated in Fig. 23-3, are diagnostic. Treatment consists of a particle repositioning maneuver (Fig. 23-4), which is highly successful and can be taught to the patient for use in future attacks. Despite the “benign” nature of benign paroxysmal positional vertigo, the initial episode often leads to emergency medical care. Since several nonbenign conditions, such as posterior fossa tumors, may present with positional dizziness, a thorough neurologic evaluation of all patients with positional vertigo is warranted.

Eighth Nerve Lesions

Eighth nerve lesions leading to neurologic manifestations include auditory neuropathy and vestibular neuronitis. Auditory neuropathy is a disorder of dysfunction or dyssynchrony of the inner hair cells or cochlear nerve, leading to hearing loss and impaired speech discrimination with intact outer hair cell function.[5] Risk factors for auditory neuropathy include prematurity, hyperbilirubinemia, and exposure to ototoxic medications, although genetic factors have also been implicated. This type of hearing loss can be associated with other neurologic diseases and may be seen in up to 11 percent of children with sensorineural hearing loss.

Vestibular neuronitis is an idiopathic inflammation of the vestibular portion of the eighth cranial nerve leading to acute symptoms of vertigo, nystagmus, nausea, and vomiting. Acute symptoms persist for several days and are often preceded by viral illness. In some patients, mild symptoms can last for weeks or months. Unilateral reduction in vestibular response is seen on caloric testing or vestibular evoked myogenic potentials. Possible etiologies include viral infection, immunologic causes, or vascular occlusion. The superior or inferior vestibular nerve, or both, may be involved.

Cerebellopontine Angle Disorders

Cerebellopontine angle masses may cause hearing loss, tinnitus, and vertigo. The most common type of mass found in this location is a vestibular schwannoma, commonly referred to as an acoustic neuroma. Symptoms are typically of insidious onset, but sudden hearing loss or vertigo may occur. Additionally, facial numbness may be seen with large tumors due to compression of the trigeminal nerve. Facial nerve dysfunction from vestibular schwannoma is uncommon. Without treatment, lower cranial nerve involvement and brainstem compression may eventually occur (Fig. 23-5). MRI of the internal auditory canal is the typical modality used to identify these lesions. Acoustic neuromas are treated with surgical excision or stereotactic radiation; small tumors may be observed for evidence of growth. Other masses occurring in the cerebellopontine angle include meningiomas, epidermoid tumors, and metastases, which may cause similar symptoms, although the time scale of symptomatology is typically more rapid with metastatic lesions in this area.

Superior Semicircular Canal Dehiscence Syndrome

Superior semicircular canal dehiscence syndrome was first recognized in 1998 as a cause of vertigo.[6] The

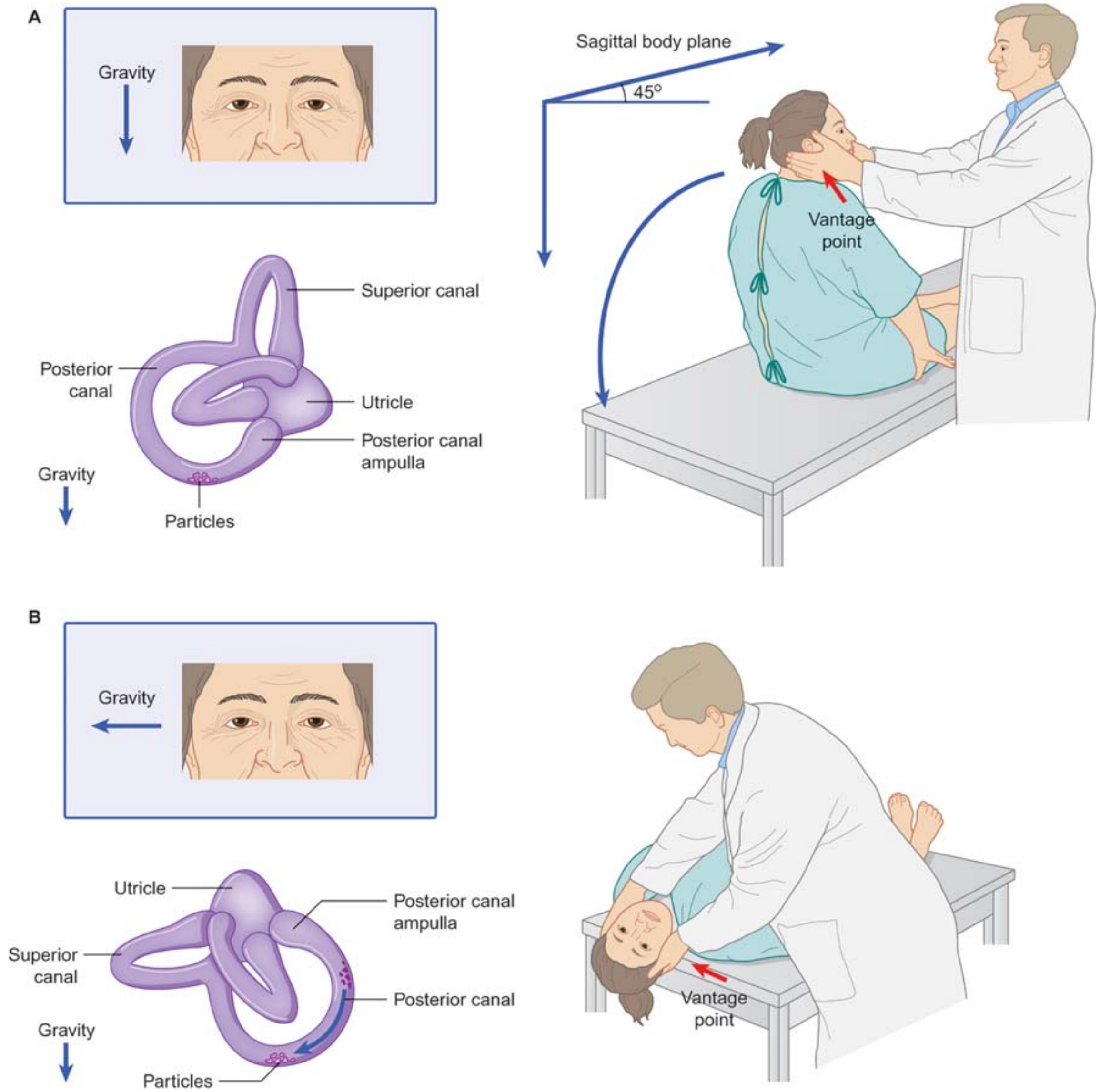
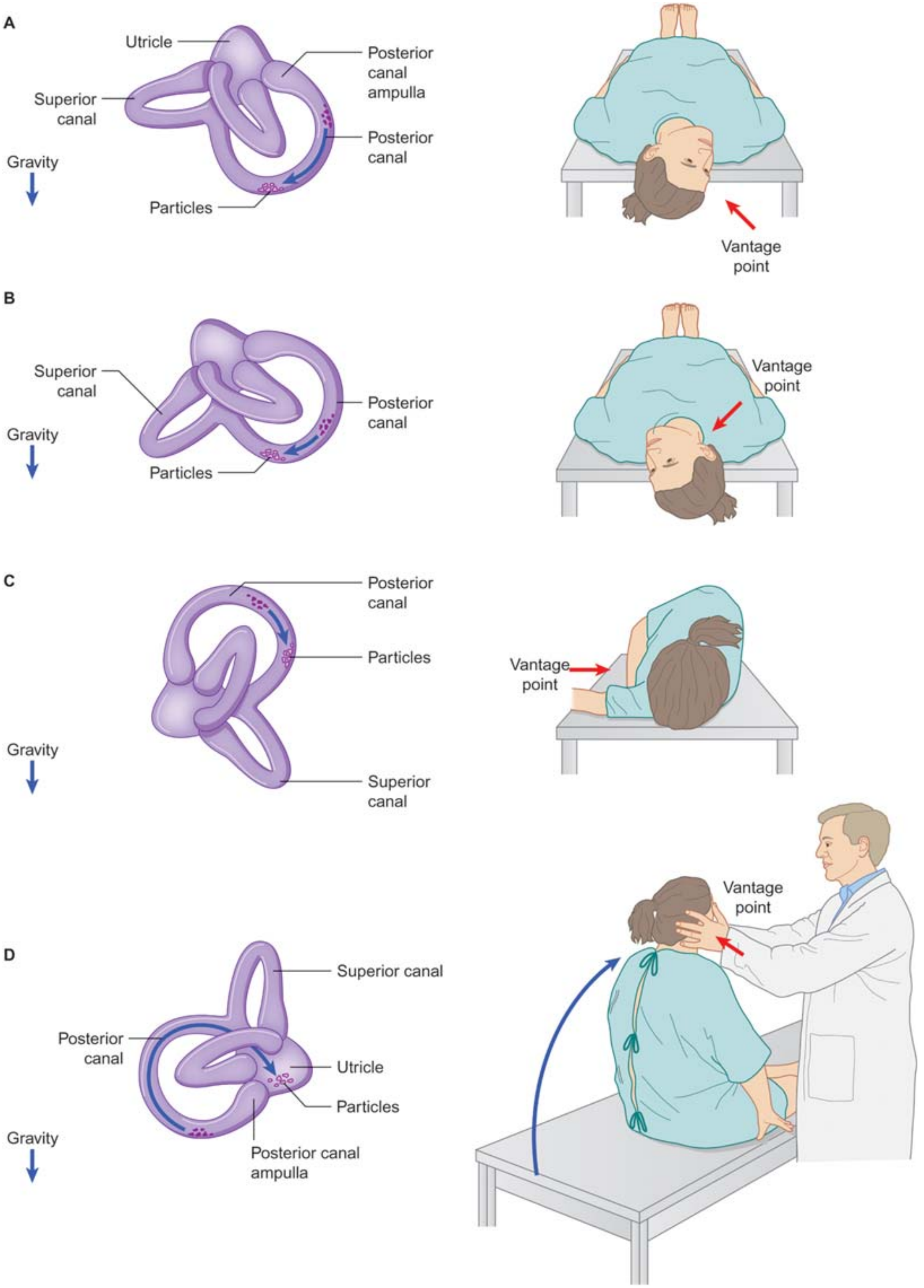

A
Gravity
Sagittal body plane
45°
Vantage point
Superior canal
Posterior canal
Utricle
Posterior canal ampulla
Gravity
Particles
B
Gravity
Utricle
Posterior canal ampulla
Superior canal
Posterior canal
Gravity
Particles
Vantage point

FIGURE 23-3 ■ Dix–Hallpike Maneuver. The Dix–Hallpike test of a patient with benign paroxysmal positional vertigo affecting the right ear. *A*, The examiner stands at the patient's right side and rotates the patient's head 45 degrees to the right to align the right posterior semicircular canal with the sagittal plane of the body. *B*, The examiner moves the patient, whose eyes are open, from the seated to the supine right-ear-down position and then extends the patient's neck so that the chin is pointed slightly upward. The latency, duration, and direction of nystagmus, if present, and the latency and duration of vertigo, if present, should be noted. The arrows in the inset depict the direction of nystagmus in patients with typical benign paroxysmal positional vertigo. The presumed location in the labyrinth of the free-floating debris thought to cause the disorder is also shown. (From Furman JM, Cass SPC: Benign paroxysmal positional vertigo. N Engl J Med 341:1590, 1999, with permission.)

disorder is caused by a defect in the bone over the superior semicircular canal, which renders the canal sound sensitive. Symptoms of superior semicircular canal dehiscence syndrome include vertigo induced by sound or pressure (such as during a Valsalva maneuver), hearing loss, and autophony. Systemic neurologic symptoms are absent. Noncontrast CT scan of the temporal bone demonstrates the absence of bone over the superior semicircular canal. Treatment consists of surgically plugging the superior canal in patients with bothersome vestibular symptoms (Fig. 23-6).

Central Vestibular Disorders

The most common central vestibular disorders include vestibular migraine, vascular disease affecting


A
Utricle
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D
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Utricle
Particles
Gravity
Posterior canal ampulla

FIGURE 23-4 ■ Particle repositioning maneuver for the bedside treatment of a patient with benign paroxysmal positional vertigo affecting the right ear. The presumed position of the debris within the labyrinth during the maneuver is shown in each panel. The maneuver is a three-step procedure. First, a Dix–Hallpike test is performed with the patient's head rotated 45 degrees toward the right ear and the neck slightly extended with the chin pointed slightly upward. This position results in the patient's head hanging to the right, *A*. Once the vertigo and nystagmus provoked by the Dix–Hallpike test cease, the patient's head is rotated about the rostral-caudal body axis until the left ear is down, *B*. Then the head and body are further rotated until the head is face down, *C*. The vertex of the head is kept tilted downward throughout the rotation. The maneuver usually provokes brief vertigo. The patient should be kept in the final, face-down position for about 10 to 15 sec. With the head kept turned toward the left shoulder, the patient is brought into the seated position, *D*. Once the patient is upright, the head is tilted so that the chin is pointed slightly downward. (From Furman JM, Cass SPC: Benign paroxysmal positional vertigo. N Engl J Med 341:1590, 1999, with permission.)

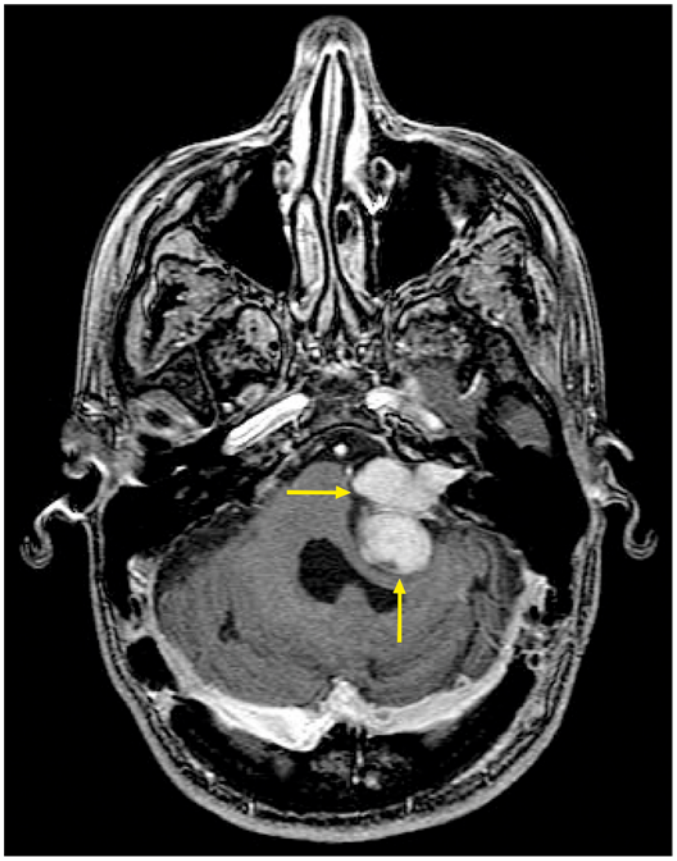

FIGURE 23-5 ■ Magnetic resonance imaging (MRI) of a large acoustic neuroma with brainstem compression. Axial contrast-enhanced T1-weighted MRI reveals a large, lobulated, enhancing mass (*arrows*) filling the left cerebellopontine angle, with compression of the pons and thinning of the brachium pontis. The patient was known to have neurofibromatosis type 2, and this lesion is most likely a schwannoma of the eighth cranial nerve. (Courtesy of Barton F. Branstetter, MD, University of Pittsburgh.)

the brainstem and cerebellar vestibular pathways, cerebellar degeneration, and Chiari malformation. Vestibular migraine, which can be considered a migraine variant, affects women more often than men, particularly women in their childbearing years. As with migraine headache, it is a diagnosis of exclusion, since there are no pathognomonic tests for this condition. Diagnostic criteria consist of a combination of the International Headache Society criteria for migraine headache and criteria developed specifically for vestibular migraine.[7] Establishing a diagnosis of vestibular migraine requires a temporal association between dizziness and either migraine headache or typical migrainous symptoms and the absence of another diagnosis that can account for the dizziness. The pathophysiology is uncertain but is likely to be related to serotonin effects on central vestibular structures. Treatment is similar to the treatment for migraine headache and includes both decreasing triggers for migraine and use of pharmacotherapy. For patients with frequent (greater than one per week) episodes of vestibular migraine, prophylactic medications are indicated to reduce the frequency and severity of attacks and include antidepressants, β-blockers, anticonvulsants, and calcium-channel blockers. Some patients may benefit from triptans for acute attacks.

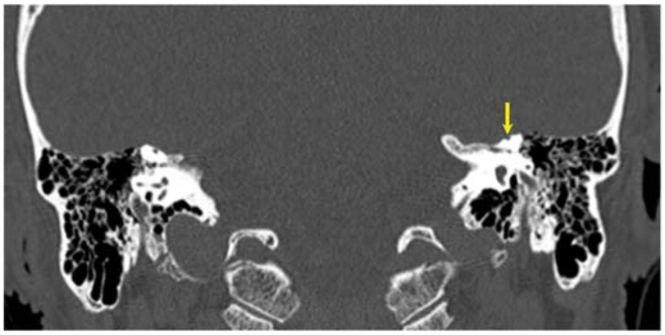

FIGURE 23-6 ■ Coronal CT scan through the level of the temporal bone demonstrating superior canal dehiscence. Arrow points to the left superior semicircular canal dehiscence. The membranous superior semicircular canal (seen in cross section) is in contact with the overlying contents of the middle cranial fossa. Compare this with the right side, where a very thin plate of bone is separating the superior semicircular canal from the middle cranial fossa. (Courtesy of Andrew A. McCall, MD, University of Pittsburgh.)

Central vestibular structures in the brainstem and cerebellum are supplied by the posterior inferior cerebellar artery and the anterior inferior cerebellar artery. Infarction of the lateral medulla in the territory of the posterior inferior cerebellar artery leads to a Wallenberg syndrome, wherein one of two vestibular nuclear complexes is damaged, leading to central vestibular imbalance. Accompanying symptoms are caused by involvement of the ascending spinothalamic tract and descending sympathetic tracts. Patients with Wallenberg syndrome may experience lateropulsion (i.e., a sense of being pushed or pulled to one side). Infarction in the territory of the anterior inferior cerebellar artery leads to a similar syndrome but may also include the presence of unilateral hearing loss resulting from cochlear ischemia because the internal auditory artery arises from the anterior inferior cerebellar artery.

Another condition to be considered in patients with acute vertigo and accompanying neurologic disturbances referable to the brainstem and cerebellum is that of cerebellar hemorrhage or infarction with concomitant brainstem compression. This condition represents a neurosurgical emergency. Brain imaging provides definitive diagnostic information.

Vertebrobasilar insufficiency may present with various neurologic symptoms including vertigo and changes in hearing as well as symptoms referable to posterior fossa structures, such as changes in vision, sensation, strength, or level of consciousness. Symptoms typically last for minutes. Isolated vertigo is rarely a result of vertebrobasilar insufficiency. Diagnostic imaging such as MR or CT angiography is helpful in establishing a diagnosis of vertebrobasilar insufficiency in the context of appropriate symptoms. Treatment with antiplatelet agents and management of risk factors for cardiovascular disease are warranted for most cases; endovascular treatment with angioplasty, stenting, or both, is rarely employed.

Cerebellar degeneration can be associated with dizziness and dysequilibrium. Some types of cerebellar degeneration (particularly spinocerebellar ataxia type 6) can also be associated with episodic features including episodic vertigo and dysequilibrium. In association with such symptoms, patients with cerebellar degeneration often demonstrate limb ataxia and sometimes long-tract signs. Chiari malformations sometimes present with "dizziness" and dysequilibrium. Physical examination may disclose downbeating nystagmus (i.e., vertical nystagmus with a downward fast component), which may reflect a central vestibular imbalance. Additionally, patients with a Chiari malformation often have nonvestibular symptoms such as dysphagia and long-tract signs. A diagnosis of a Chiari malformation can be confirmed by sagittal MRI (Fig. 23-7). Treatment is surgical and involves suboccipital craniotomy.

Central Auditory Processing Disorder

Central auditory processing disorder, as its name implies, is characterized by defects in higher-level processing of auditory information in the setting of normal hearing as measured by conventional audiometry. This disorder leads to difficulty in understanding oral communication, particularly when there is background noise, and can be associated with attention deficit–hyperactivity disorder, learning disabilities, head trauma, and other neurologic disorders. Psychoacoustic testing often identifies specific deficits that correlate with patients' symptoms.[8] Treatment consists of improving the signal-to-noise ratio by reduction of background noise or use of FM systems, as well as auditory training.[9]

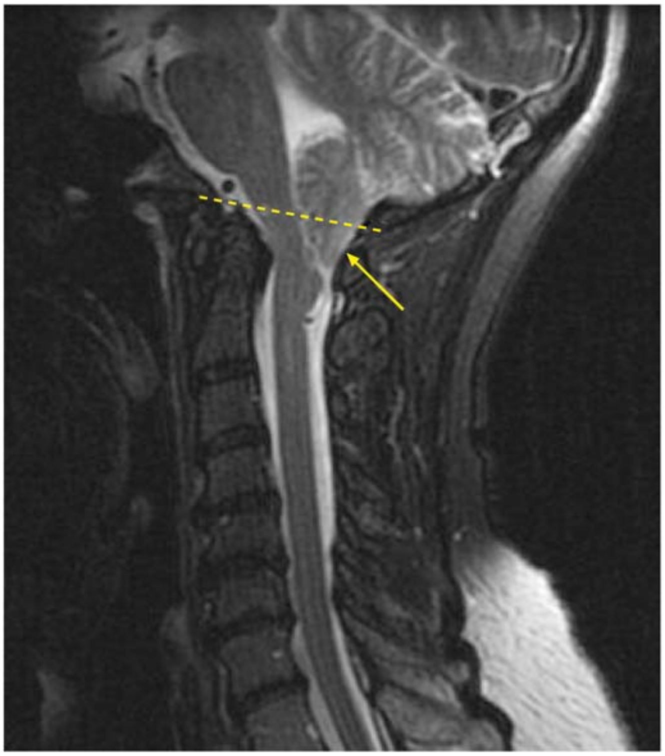

FIGURE 23-7 ■ Chiari malformation. Sagittal T2-weighted MRI through the cranio-cervical junction shows the cerebellar tonsils (*solid arrow*) extending far below the foramen magnum (*dashed line*). The medulla is compressed. (Courtesy of Barton F. Branstetter, MD, University of Pittsburgh.)

OTONEUROLOGIC MANIFESTATIONS OF SYSTEMIC DISEASE

Infection

Many infections can cause otoneurologic symptoms and signs. Viral infection, in particular herpes simplex virus, has been implicated in Bell palsy. Fig. 23-8 shows herpes simplex virus type 1 particles seen by electron microscopy in the geniculate ganglion of

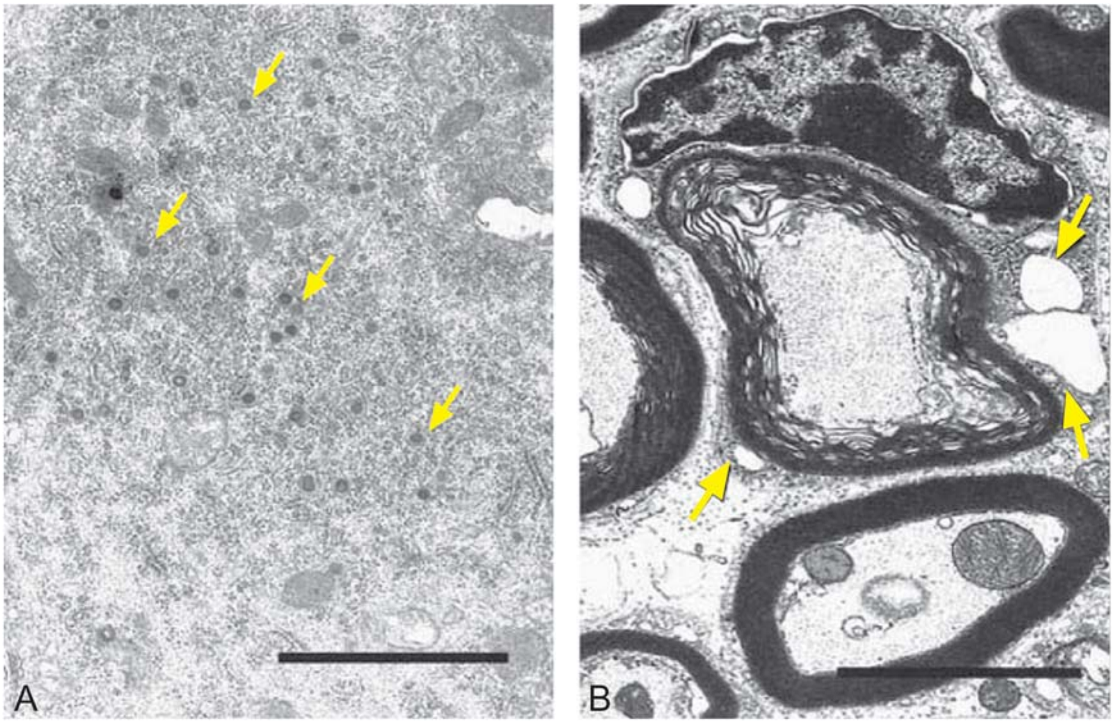

FIGURE 23-8 ■ Herpes simplex virus (HSV) in a mouse model of Bell palsy. *A*, The intratemporal portion of the facial nerve from the paralyzed side showing a neuron in the geniculate ganglion. Replicating HSV-1 viruses in the rough endoplasmic reticulum of a neuron in the geniculate ganglion are indicated by the arrows. *B*, The geniculate portion of the facial motor nerve. Arrows indicate vacuolar changes in the cytoplasm of a Schwann cell which resulted in demyelination. Scale bars: *A*, 1 μm; *B*, 5 μm. (From Takahashi H, Hitsumoto Y, Honda N, et al: Mouse model of Bell's palsy induced by reactivation of herpes simplex virus type 1. J Neuropathol Exp Neurol 60:621, 2001, with permission.)

mice with experimentally induced Bell palsy. Corticosteroids are used for treatment. Viral infection is also thought to play a role in idiopathic sudden sensorineural hearing loss and vestibular neuronitis. Mumps, measles, and congenital rubella infection may cause significant hearing loss.

Another member of the herpes virus family, varicella-zoster virus, causes herpes zoster oticus, often referred to as Ramsay Hunt syndrome. This syndrome, from reactivation of varicella-zoster virus in the geniculate ganglion, is characterized by facial weakness associated with vesicular lesions in the external auditory canal and auricle. The symptoms are typically preceded by otalgia. Sensorineural hearing loss and vertigo are sometimes present. Investigators have postulated that the reactivation of varicella-zoster virus may occur in the vestibular and spiral ganglia as well. Ramsay Hunt syndrome may involve other cranial nerves; polymerase chain reaction has localized viral material to the CSF in some cases. MRI typically reveals enhancement of the geniculate ganglion on the affected side. Treatment is with antiviral agents and corticosteroids. The facial palsy associated with Ramsay Hunt syndrome has a poorer prognosis than that of Bell palsy.[10]

Otosyphilis was first described in 1887 by Politzer. Following the introduction of penicillin, it became rare. However, with the emergence of human immunodeficiency virus (HIV) infection, syphilis has experienced a resurgence in the United States and Western Europe. Otoneurologic manifestations may occur in secondary, tertiary, or congenital syphilis. Sensorineural hearing loss and hydropic symptoms of episodic tinnitus and vertigo may occur. Treatment is with penicillin G and corticosteroids.

Lyme disease may cause sudden sensorineural hearing loss or facial palsy. Vertigo is uncommon but has been reported. The mainstay of treatment is antibiotics, most typically doxycycline.

Tuberculosis may affect the ear. As with syphilis, tuberculosis has become increasingly common in patients with HIV infection. Tuberculous otitis media remains rare. The classic description of mycobacterial otitis media is of chronic otorrhea and multiple perforations of the tympanic membrane. Polyps and granulation tissue may also be seen. Treatment is primarily medical, with surgery reserved for complications.

HIV infection and immunodeficiency may cause otologic symptoms. Otitis externa may be caused by common pathogens such as *P. aeruginosa*; however, opportunistic infections such as *Pneumocystis* species may also be responsible in these populations. There are also reports of malignant otitis externa (i.e., skull base osteomyelitis secondary to otitis externa) in individuals with HIV infection, although some authors note that the incidence of malignant otitis externa is not increased in the HIV-infected population as a whole. Children with HIV infection often suffer from chronic otitis media. Serous otitis media may result from eustachian tube obstruction secondary to adenoid hypertrophy. Sensorineural hearing loss occurs in 21 to 49 percent of HIV-positive patients and is thought to be multifactorial. Possible causes include secondary infection, central nervous system (CNS) involvement, and ototoxicity. Finally, facial palsy is more common in HIV-positive patients.

Immune-Mediated and Connective Tissue Disease

There are a number of autoimmune and connective tissue disorders that cause otoneurologic symptoms, ranging from otitis media to hearing loss or vertigo.

Granulomatosis with polyangiitis (GPA; previously Wegener granulomatosis) is characterized by vasculitis of medium-sized and small vessels, as well as by necrotizing granulomas of the upper and lower respiratory tract. Up to 70 percent of patients with this disorder experience otologic symptoms. The most common otoneurologic manifestation of GPA is serous otitis media. The middle ear space can be affected by granulomas, leading to a clinical picture resembling chronic suppurative otitis media (Fig. 23-9). Facial palsy may also result, from either vasculitis or direct involvement of the facial nerve by the granulomatous process. Sensorineural hearing loss occurs in 8 percent of patients and is sometimes rapidly progressive. Vertigo is uncommon. GPA is diagnosed by the presence of cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) and by the combination of necrotizing granulomas and vasculitis seen on histopathology. Treatment is with high-dose corticosteroids and immunosuppressive agents.

Sarcoidosis is an immune-mediated disease of unknown etiology characterized by hilar adenopathy, pulmonary infiltrates, peripheral lymphadenopathy, and cutaneous and splenic involvement that can involve the CNS. The characteristic histopathologic finding is of noncaseating granulomas, although they are nonspecific. The most common otoneurologic manifestation of sarcoidosis is facial palsy, which may be unilateral or bilateral and can be associated with parotiditis, fever, and uveitis (uveoparotid fever or Heerfordt disease). Multiple cranial nerve palsies are common in neurosarcoidosis, occurring in approximately 5 percent of patients with sarcoidosis due to involvement of the meninges of the skull base. Hearing loss and vertigo are less common symptoms. The presentation of hearing loss is variable, ranging from mild to severe, and may be unilateral or bilateral. Vestibular testing may be abnormal. Auditory and vestibular symptoms are thought to reflect involvement of the eighth cranial nerve by neurosarcoidosis rather than a direct effect on the inner ear end organs. Contrast-enhanced MRI may show enhancement of the basal leptomeninges; intracranial mass lesions can also be seen.

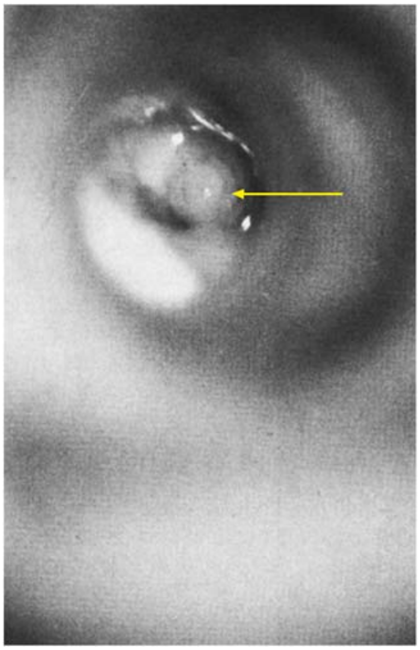

FIGURE 23-9 ■ Chronic otitis media in granulomatosis with polyangiitis. Granulomatous swelling of the posterior part of the left eardrum viewed through an otomicroscope (*arrow*). The large white area inferior and to the left of the eardrum is the anterior wall of the external ear canal. (From Rasmussen N: Ear, nose and throat manifestations in c-ANCA positive vasculitides. Ann Med Interne 143:401–404 1992.)

Systemic lupus erythematosus may cause sensorineural hearing loss that is unilateral or bilateral in 8 to 31 percent of patients and can be rapidly progressive.[11] The hearing loss appears to be associated with elevated anticardiolipin antibodies but not with ANA titer and frequently improves with treatment.[11] Vestibular symptoms are less common.

Other immune-mediated diseases causing otologic symptoms include polyarteritis nodosa, Cogan syndrome, Behçet syndrome, relapsing polychondritis, Sjögren syndrome, and Churg–Strauss syndrome. Polyarteritis nodosa, a small-vessel vasculitis, may cause sudden sensorineural hearing loss. Cogan syndrome is characterized by sudden or rapidly progressive sensorineural hearing loss, vestibular dysfunction, and interstitial keratitis, mimicking syphilis, or Meniere disease. Symptoms often respond to treatment with corticosteroids. Behçet syndrome may cause hearing loss, tinnitus, and vertigo. Relapsing polychondritis typically involves the cartilage of the external ear and nose; however, as the disease progresses, hearing loss and vertigo sometimes develop. The disorder is discussed further in Chapter 22. High-frequency hearing loss may also be seen in 25 percent of patients with Sjögren syndrome. Churg–Strauss syndrome causes hearing loss in rare instances.[11]

Autoimmune hearing loss also may occur in the absence of systemic illness. It is characterized by fluctuating or rapidly progressive bilateral sensorineural hearing loss that is responsive to immunosuppressive therapy.

Neurocutaneous Syndromes

The most common neurocutaneous syndrome causing otoneurologic symptoms is neurofibromatosis type II (NF2), which is discussed in detail in Chapter 21. This disease is characterized by bilateral vestibular schwannomas, eventually causing bilateral deafness and vestibular dysfunction. Other features of neurofibromatosis type II can include meningiomas, ependymomas, gliomas, and juvenile posterior subcapsular lens opacities.[12] Otologic manifestations consist of progressive hearing loss that may be unilateral or bilateral, tinnitus, vestibular dysfunction, and facial weakness. Genetic testing is available to detect mutations in the neurofibromin 2 (*merlin*) tumor suppressor gene.[12] Auditory rehabilitation of affected patients is complex owing to the presence of bilateral acoustic neuroma; auditory brainstem implants have been used in this population with fair results.

Metabolic and Endocrine Disorders

Certain metabolic or endocrine disorders are known to contribute to hearing loss. Diabetes mellitus has been linked to hearing loss, perhaps secondary to microangiopathy and neuropathy. A small subset of diabetic patients has been found to have a mitochondrial mutation causing both hearing loss and diabetes, termed maternally inherited diabetes and deafness (MIDD).[13] The same mitochondrial mutation responsible for MIDD can also result in mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS). Diabetic patients frequently suffer from "dizziness" and imbalance, and peripheral neuropathy, autonomic dysfunction, and peripheral vestibular deficits all probably play a role in etiology.

Renal failure in the absence of diabetes is also associated with high-frequency hearing loss. Alport syndrome is characterized by congenital hearing loss and renal failure. Neonatal jaundice may cause sensorineural hearing loss. Hyperlipidemia has also been associated with fluctuating hearing loss and vestibular dysfunction.

An association between thyroid disease and otologic symptoms exists. Vertigo and hearing loss have been described in the setting of hypothyroidism. Pendred syndrome is characterized by congenital hearing loss, reduced vestibular responses, and goiter. In a study of 42 kindreds, resistance to thyroid hormone was found to be associated with hearing loss in 21 percent of individuals.

Certain mucopolysaccharidoses are associated with hearing loss, and many forms predispose to otitis media. The Hurler and Hunter forms (MPS I and II) cause sensorineural hearing loss. The mechanism of loss is unclear and may involve deposition of glycosaminoglycans in the cochlea.

Diseases of Bone

Several disorders of bone, discussed in Chapter 22, lead to otoneurologic manifestations, most notably hearing loss. These include osteogenesis imperfecta, Paget disease, fibrous dysplasia, and osteopetrosis.

Osteogenesis imperfecta is usually an autosomal-dominant disease caused mainly by mutations in the *COL1A1* or *COL1A2* genes, which code for type 1 collagen. The disorder is characterized by fragility of bones, hearing loss, and blue sclera. Eight major types are currently described; hearing loss is most

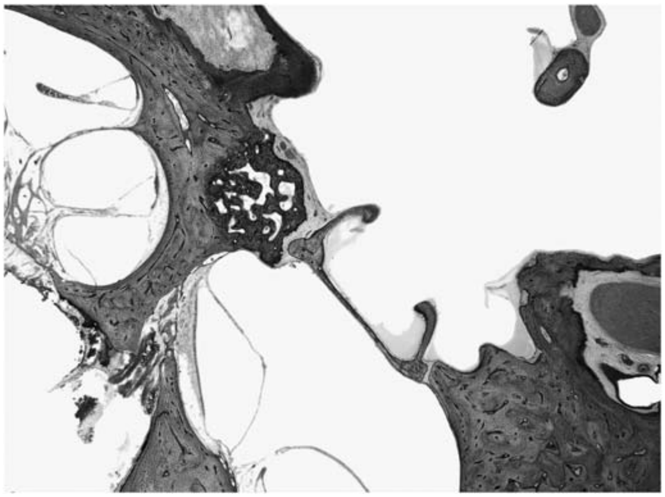

FIGURE 23-10 ■ Osteogenesis imperfecta of the temporal bone. Histologic section of the right temporal bone from a patient with osteogenesis imperfecta, showing an otosclerotic lesion anterior to the oval window. (From Santos F, McCall A, Chein W, et al: Otopathology in osteogenesis imperfecta. Otol Neurotol 33:1562, 2012, with permission.)

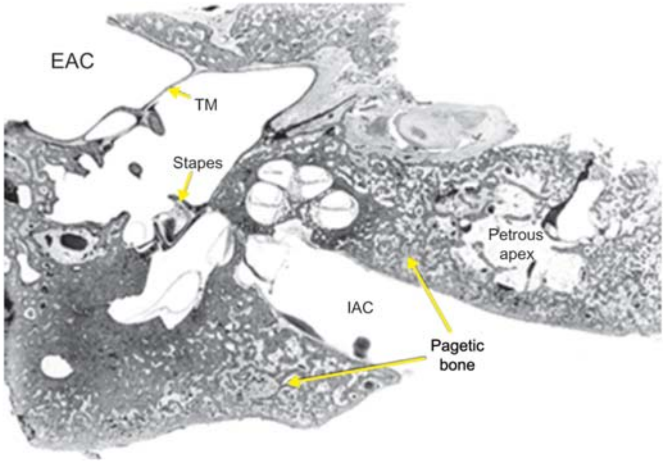

FIGURE 23-11 ■ Paget disease of the temporal bone. Histologic section through the left temporal bone showing pagetic bone surrounding the internal auditory canal. (From Bahmad F Jr, Merchant SN: Paget disease of the temporal bone. Otol Neurotol 28:1157, 2007, with permission.)

common in types IA and IB. Hearing loss occurs in 23 to 58 percent of patients with osteogenesis imperfecta and typically presents in the second or third decade.[14] Histologic examination of temporal bones from individuals with type I osteogenesis imperfecta demonstrates otosclerosis-like lesions (Fig. 23-10). The hearing loss typically begins as a conductive loss and progresses to become mixed or largely sensorineural in nature; both ears are eventually affected. Hearing loss may be treated with amplification or stapedectomy. Tinnitus and vertigo are also common in osteogenesis imperfecta, particularly in those patients with sensorineural hearing loss. Vertigo is typically mild, triggered by head movements or position change, and brief in duration. Abnormalities are frequently seen on electronystagmography but do not necessarily correlate with subjective vertigo.

Paget disease is caused by increased bone absorption and repair, leading to an overall increase in the amount of bone. There are monostotic and polyostotic forms. Hearing loss is common in Paget disease and is usually mixed conductive and sensorineural. Conductive hearing loss may be caused by ossicular fixation or obliteration of the oval or round window. Bony changes in the cochlea may also contribute. Involvement of the petrous portion of the temporal bone may alter the shape of the internal auditory canal, potentially impairing the function of the eighth cranial nerve. Histologically, Paget disease is characterized by disordered lamellar bone (Fig. 23-11). CT may reveal demineralization of the temporal bone. Treatment is with bisphosphonates and calcitonin, which may prevent further hearing loss.

Fibrous dysplasia, like Paget disease, also has monostotic and polyostotic forms. In its polyostotic form it can also be associated with café-au-lait spots on the skin and endocrinopathies in a syndrome designated McCune–Albright syndrome. McCune–Albright syndrome is nonfamilial but usually caused by mutations in the *GNAS* gene, which codes for a second messenger G protein. The disease is characterized by expansile bony lesions (Fig. 23-12). Involvement of the temporal bone can cause narrowing of the external auditory canal, resulting in conductive hearing loss. A lesser percentage of patients will manifest sensorineural hearing loss, labyrinthitis, dizziness, or facial weakness.[15] Treatment is with bisphosphonates or surgical resection. Irradiation increases the risk of malignant transformation and is not indicated.

Osteopetrosis is characterized by decreased osteoclastic activity, leading to constriction of various skull base foramina. Hearing loss, vertigo, and facial palsy or spasm may develop secondary to compression. Eustachian tube dysfunction and middle ear effusions may be seen. Treatment is with vitamin D (calcitriol), prednisone, and interferon-gamma.

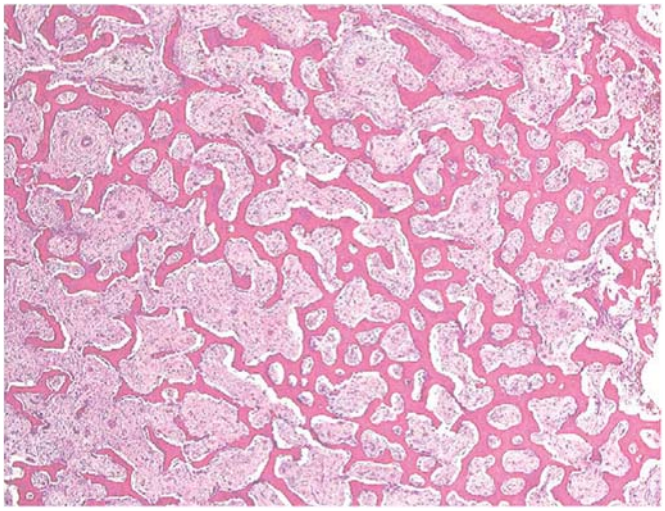

FIGURE 23-12 ■ Histology of fibrous dysplasia. Note the irregular shapes of woven bone. (From Speight PM, Carlos R: Maxillofacial fibro-osseous lesions. Curr Diagn Pathol 12:1, 2006, with permission.)

Drug-Induced Disorders

There are numerous medications that exert ototoxic effects on the cochlea and labyrinth. The most commonly encountered ototoxic medications are chemotherapeutic agents, antibiotics, and loop diuretics. Cochlear ototoxicity is typically heralded by tinnitus or a sense of fullness in the ear; however, high-frequency hearing loss may also occur without the patient's knowledge. Hearing loss due to certain drugs, most notably salicylates and furosemide, can be reversible, whereas toxicity secondary to cisplatin and aminoglycosides is most often permanent. Vertigo and disequilibrium may result from vestibular toxicity; bobbing oscillopsia is a common symptom.[16] Conditions contributing to a higher risk for ototoxicity include renal insufficiency, hepatic insufficiency, elevated serum levels of medication, pre-existing hearing loss or vestibular dysfunction, use of multiple ototoxic medications or a previous history of ototoxic medication use, treatment for more than 14 days, prior exposure to noise, hypovolemia, bacteremia, fever, and age over 65 years.[16]

Ototoxicity leads to distinct histologic changes within the cochlea and labyrinth, and the histologic manifestations are typically either hair cell loss (Fig. 23-13) or changes in the stria vascularis.

Aminoglycoside antibiotics have been known to be ototoxic since the parenteral use of streptomycin for tuberculosis in the early twentieth century. Symptomatic hearing loss occurs in 2 to 14 percent of patients treated with aminoglycosides; however, high-frequency (10 to 20 kHz) audiometry reveals the incidence of hearing loss to be as high as 62 percent. Certain aminoglycosides, such as streptomycin and gentamicin, preferentially lead to vestibular toxicity but also cause cochlear toxicity. It is unclear whether elevated serum levels of antibiotic correlate with increased risk of toxicity. The pathogenesis is thought to involve generation of free radicals leading to apoptosis of hair cells. There is evidence that certain mitochondrial mutations cause increased susceptibility to the ototoxic effects of aminoglycosides. Other anti-infective agents reported to cause ototoxicity less frequently include vancomycin, macrolides, fluoroquinolones, tetracycline, antivirals, amphotericin, flucytosine, and antimalarials.

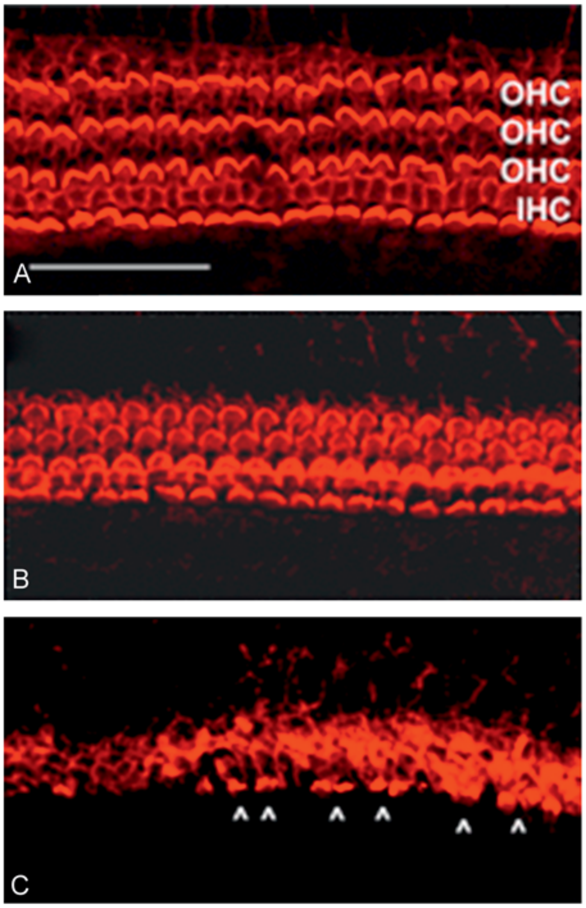

FIGURE 23-13 ■ Hair cell loss from gentamicin ototoxicity. *A* and *B* demonstrate a normal complement of inner (IHC) and outer hair cells (OHC) of the cochlea. *C* shows severe loss of outer hair cells and many inner hair cells after exposure to gentamicin (mouse cochlea). (From Matt T, Ng CL, Lang K, et al: Dissociation of antibacterial activity and aminoglycoside ototoxicity in the 4-monosubstituted 2-deoxystreptamine apramycin. Proc Natl Acad Sci USA 109:10988, 2012, with permission.)

Cisplatin is the chemotherapy agent most frequently associated with ototoxicity, with an incidence of 20 to 65 percent. Hearing loss initially manifests in the high frequencies and progressively worsens with continued administration. Tinnitus is a common presenting complaint. Ototoxicity appears related to the cumulative dose. Histologic findings in cisplatin ototoxicity include damage to the stria vascularis and hair cell loss. Ongoing studies are evaluating agents that may protect against cisplatin-induced ototoxicity. Owing to the high incidence of ototoxicity with aminoglycosides and cisplatin, patient monitoring with high-frequency audiometry and careful attention to symptoms is recommended for early diagnosis and management. Other ototoxic chemotherapeutic agents include carboplatin, oxiliplatin, vinca alkaloids, bexarotene, and taxanes.

Loop diuretics can cause hearing loss, tinnitus, and occasionally vertigo, perhaps because disturbances in the sodium and potassium concentrations in endolymph cause edema of the stria vascularis. Hearing loss is typically reversible and is usually seen with parenteral rather than oral administration of the offending medication. Bumetanide may be less ototoxic than furosemide or ethacrynic acid.

Salicylates can cause tinnitus and reversible hearing loss, although some cases of permanent hearing impairment have been reported following overdoses.

Environmental Disorders

Numerous types of environmental injury can result in otoneurologic symptoms. Noise exposure is well known to cause hearing loss. The typical audiometric configuration is a sensorineural hearing loss with a notched pattern around 4000 Hz. Both occupational and recreational exposure can cause significant loss. Some individuals appear more likely than others to sustain noise-induced loss. The best treatment of noise-induced hearing loss is prevention. Hearing protection with earplugs or earmuffs can decrease exposure to sound. Maximum allowable amount and duration of noise exposure are available through the Occupational Health and Safety Administration (OSHA). The National Institute of Occupational Safety and Health (NIOSH) also has guidelines on the amount and duration of exposure that are safe, but the levels differ between the two agencies.

Barotrauma may cause otologic injury through multiple mechanisms. The most common injury is perforation of the tympanic membrane. Barotrauma may also lead to conductive hearing loss from fracture or dislocation of the ossicles. Rarely, facial nerve paresis can result. Inner ear barotrauma can manifest as a perilymphatic fistula, manifest by hearing loss, vertigo, nausea, and vomiting following exposure to increased atmospheric pressure. Inner ear decompression sickness causes similar symptoms, usually manifesting itself after surfacing from a dive. The prognosis for recovery is good for inner ear barotrauma, but progressive damage to the cochlear and vestibular organs often occurs following inner ear decompression sickness.

Lightning strikes have also been documented to have otoneurologic sequelae. Lightning may produce injury either through a direct strike or over telephone lines. Hearing loss, tinnitus, tympanic membrane perforation, facial palsy, and vertigo have been reported. Hearing loss is nonprogressive and may have a mixed conductive and sensorineural pattern.

Blast injuries to the ear may lead to tympanic membrane rupture and resulting conductive hearing loss. Sensorineural hearing loss is also common and appears to occur via a different mechanism from noise-induced hearing loss, as the audiometric pattern lacks a notch at 4000 Hz. Tinnitus can result from blast injury and may be particularly noticeable in that disorder because of its sudden onset.[17] Balance disorders can also manifest following blast and mild traumatic brain injury.

Severe thermal injury to the ear may result from slag burns from welding. Often nonhealing perforations of the tympanic membrane are seen. Facial paralysis, sensorineural hearing loss, and vertigo have also been reported.

Nutritional Disease

Wernicke encephalopathy, which results from hypovitaminosis B_1 (thiamine), manifests with ataxia, abnormal eye movements, and mental status change. Vestibular laboratory testing of patients with Wernicke encephalopathy typically indicates bilaterally reduced vestibular responses and abnormal central vestibular processing. Treatment is by replacement of thiamine, which usually corrects the abnormal eye movements and ataxia. Vestibular function remains abnormal.

Neoplastic Disease

The temporal bone is affected by primary malignancies as well as metastatic disease. Primary tumors may

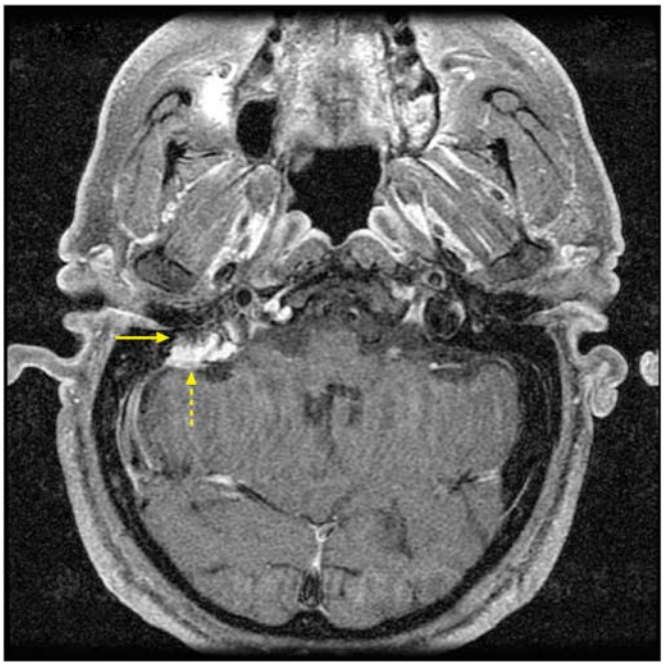

FIGURE 23-14 ■ MRI of endolymphatic sac tumor. Axial contrast-enhanced T1-weighted MRI demonstrates an irregular, enhancing mass along the posterior border of the petrous apex, at the expected location of the endolymphatic sac (*dashed arrow*). The mass erodes into the underlying temporal bone (*solid arrow*). (Courtesy of Barton F. Branstetter, MD, University of Pittsburgh.)

originate in the external ear, middle ear and mastoid, or inner ear structures. Squamous cell carcinoma and basal cell carcinoma can arise from the auricle and external auditory canal or they may spread from adjacent sites. Pain is a common complaint, although hearing loss and facial weakness may also occur.[18] Rhabdomyosarcoma may originate in the temporal bone in children. Endolymphatic sac tumors occur both sporadically and associated with von Hippel–Lindau disease (Fig. 23-14). Symptoms arise from local extension of the tumor and may include pain, hearing loss, and, less commonly, vertigo. Cancers of the breast, kidney, lung, stomach, thyroid gland, and prostate all may metastasize to the temporal bone.[18]

NEURO-OTOLOGIC MANIFESTATIONS OF AGING

Dysequilibrium of Aging

Dysequilibrium of aging refers to a loss of balance in association with advanced age in individuals who have no other known etiology for their balance disturbance. Patients with dysequilibrium of aging are generally in their seventies and demonstrate white matter disease on MRI including periventricular and subcortical white matter disease (Fig. 23-15) that may relate to microvascular ischemic changes. Treatment consists of managing risk factors for cerebrovascular disease and balance therapy. Vestibular-suppressant medications should be discontinued.

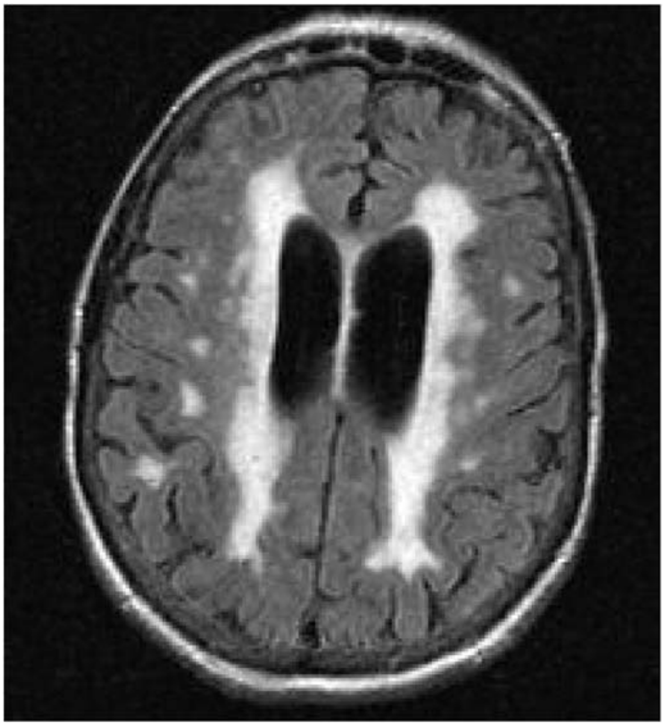

FIGURE 23-15 ■ MRI of a patient with microvascular disease seen in disequilibrium of aging. Axial fluid-attenuated inversion recovery sequence through the bodies of the lateral ventricles shows extensive, confluent areas of abnormal signal in a periventricular and subcortical distribution, consistent with white matter microvascular disease. The ventricles are slightly enlarged from associated central volume loss. (Courtesy of Barton F. Branstetter, MD, University of Pittsburgh.)

Presbycusis

Sensorineural hearing loss related to aging is termed presbycusis. Approximately one-third of persons between the ages of 60 and 70, and up to half of those between 70 and 80, have hearing loss.[10] Four subtypes of presbycusis have been described, relating to different audiometric patterns. The most common type is called sensory presbycusis, manifesting as a

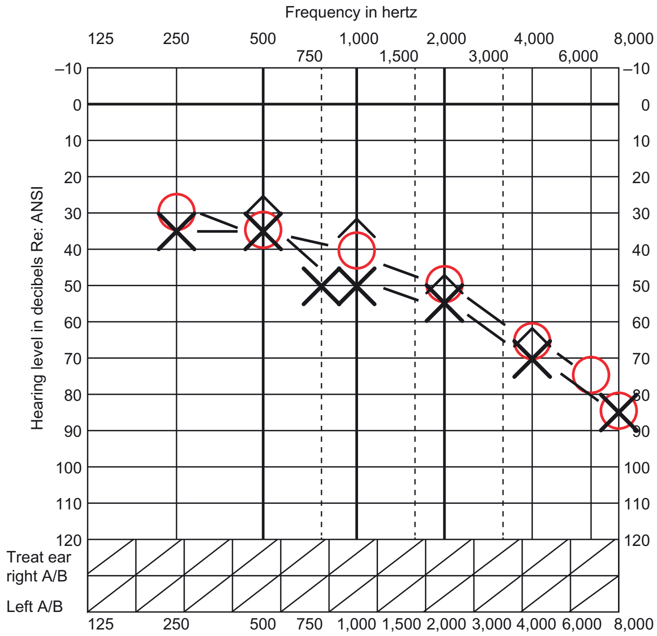

FIGURE 23-16 ■ Audiogram of presbycusis. This audiogram shows sensorineural hearing loss in a downsloping pattern, typical of presbycusis.

symmetric high-frequency sensorineural hearing loss that progressively worsens with age (Fig. 23-16). Primary synaptic degeneration is believed to play a role in the early stages of age-related hearing loss where no deficits are seen on audiometry, but patients experience hearing-in-noise deficits.[19] Both genetic and environmental factors play a role in etiology. Patients typically complain of difficulty understanding speech, especially in the presence of background noise. They may also suffer from tinnitus.

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CHAPTER

24

Neuro-Ophthalmology in Medicine

SASHANK PRASAD

AFFERENT VISUAL DISTURBANCES
- Optic Neuropathy
  - *Inflammatory Demyelinating Optic Neuritis*
  - *Neuromyelitis Optica*
  - *Ischemic Optic Neuropathy*
  - *Compressive Optic Neuropathy*
  - *Genetic Optic Neuropathy*
  - *Papilledema*
- Idiopathic Intracranial Hypertension
- Retrochiasmal Vision Loss

EFFERENT VISUAL DISTURBANCES
- Clinical Assessment
- Supranuclear Causes of Ocular Dysmotility
- Ocular Motor Nuclei and Nerves
  - *Oculomotor Nerve (III) Palsy*
  - *Trochlear Nerve (IV) Palsy*
  - *Abducens Nerve (VI) Palsy*
  - *Multiple Ocular Motor Nerve Palsies*
  - *Miller Fisher Syndrome*
- Internuclear Ophthalmoplegia
- Neuromuscular Junction Dysfunction
- Mechanical Causes of Diplopia
- Nystagmus and Other Abnormal Eye Movements
  - *Gaze-Evoked Nystagmus*
  - *Peripheral Vestibular Nystagmus*
  - *Central Vestibular Nystagmus*
  - *See-Saw Nystagmus*
  - *Congenital Nystagmus*
  - *Saccadic Intrusions*
  - *Other Ocular Movements*

THE PUPIL
- Anatomy
- The Near Response
- Anisocoria
  - *Physiologic Anisocoria*
  - *Transient Anisocoria*
  - *Horner Syndrome*
  - *Anisocoria Greater in Light With Abnormal Pupillary Light Reaction*
  - *Tonic Pupil*

Perhaps more than any other realm of neurology, neuro-ophthalmologic disorders require a systematic approach that emphasizes precise localization guided by the patient's history followed by confirmation with specific examination maneuvers. To this end, the neurologist should be familiar with specialized techniques concerning fundus examination, eye movements and alignment, and pupillary assessment in order to examine patients properly and guide their evaluation.

AFFERENT VISUAL DISTURBANCES

Afferent neuro-ophthalmologic disorders may be limited to the eye (e.g., optic neuropathy), may be secondary to a primary neurologic disorder (e.g., papilledema from an intracranial tumor), or may be related to a systemic medical disorder (e.g., giant-cell arteritis). The neuro-ophthalmologic examination provides a window to the diagnosis and natural history of the variety of medical conditions that present with afferent disturbances (Table 24-1).

Optic Neuropathy

The optic nerve is approximately 50 mm in length and is anatomically separated into intraocular, intraorbital, intracanalicular, and intracranial portions. Damage to the optic nerve can occur anywhere along its course, and optic neuropathy may result from ischemic, demyelinating, compressive, genetic, infiltrative, nutritional, traumatic, or toxic causes (Table 24-2).

The term "optic neuritis" should not be used to describe any type of optic neuropathy, but should be

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TABLE 24-1 ■ Selected Manifestations of Neuro-Ophthalmologic Disease Across the Spectrum of Organ Systems

Organ System	Disease State	Example of Neuro-Ophthalmologic Manifestation
Psychiatry	Conversion disorder	Functional blindness
Hematology	Sickle cell disease	Retrobulbar ischemic optic neuropathy
Cardiovascular	Endocarditis	Embolic retinal artery occlusion
Pulmonary	Pulmonary hypertension	Papilledema
Renal	Chronic renal failure	Intracranial hypertension
Gastrointestinal	Pancreatitis	Purtscher syndrome
Genitourinary	Ovarian cancer	Paraneoplastic syndromes with cerebellar degeneration (e.g., with anti-Yo antibodies)
Endocrine	Graves disease	Compressive optic neuropathy due to increased orbital fat content and enlarged extraocular muscles
Obstetric	Eclampsia	Cerebral blindness from posterior reversible encephalopathy syndrome (PRES)

TABLE 24-2 ■ Classification of Optic Neuropathy

Category	Prototypic Examples	Comment
Inflammatory/demyelinating	Optic neuritis	Usually associated with multiple sclerosis or neuromyelitis optica
Paraneoplastic	CRMP5, an autoantibody directed against collapsin response mediator protein	Reported with small cell lung cancer, lymphoma, nasopharyngeal carcinoma, and neuroblastoma
Infectious	Tuberculosis, cryptococcosis, human herpesvirus 6 infection, *Bartonella* infection	These infections causing optic neuropathy should prompt evaluation for infection with human immunodeficiency virus
Ischemic	Ischemic optic neuropathy (arteritic and nonarteritic), retinal artery occlusion (central or branch)	Funduscopy may show occlusive material (Hollenhorst plaque) in retinal artery occlusions
Compressive	Optic nerve sheath meningioma, Graves ophthalmopathy	Proptosis (exophthalmos) often present
Infiltrative	Sarcoidosis, metastasis, lymphoma	Orbit MRI often shows persistent enhancement of the optic nerve
Traumatic	Direct (penetrating) trauma, indirect trauma (often frontal or midfacial), or chiasmal	Injury due to compression, avulsion, or shear injury. No evidence-based guidelines regarding optimal treatment
Nutritional	Deficiency of vitamin B_1, B_2, B_{12}, or folate	Slowly progressive, symmetric optic neuropathy. Does not present acutely
Toxic	Ethambutol, carbon monoxide, methanol, tobacco-alcohol amblyopia, amiodarone	Typically bilateral and symmetric. May improve with removal of offending agent
Hereditary	Leber, Kjer (dominant optic atrophy) optic neuropathies	Leber hereditary optic neuropathy is transmitted via maternally inherited mitochondrial mutation

reserved to denote the inflammatory, demyelinating optic neuropathy that is either idiopathic or related to demyelinating disease such as multiple sclerosis (MS) or neuromyelitis optica (NMO). Inflammatory or infectious optic neuropathies from other known etiologies are best described in specific terms (e.g., sarcoid or syphilitic optic neuropathy).

Optic neuropathy may be classified anatomically as bulbar/anterior (usually associated with acute disc edema) or retrobulbar (i.e., posterior to the globe without disc swelling) (Fig. 24-1). Any cause of optic neuropathy that results in loss of axons will eventually produce optic atrophy, appearing on funduscopic examination as visible nerve fiber layer loss and disc pallor (Fig. 24-2). Optical coherence tomography is a noninvasive means of quantifying retinal nerve fiber layer atrophy or elevation and is more sensitive to detect axonal loss of the optic nerve. The presence of a relative afferent pupillary defect on the swinging flashlight test can be an important clue to the presence of optic nerve dysfunction, although this finding can also occur with significant asymmetric retinal

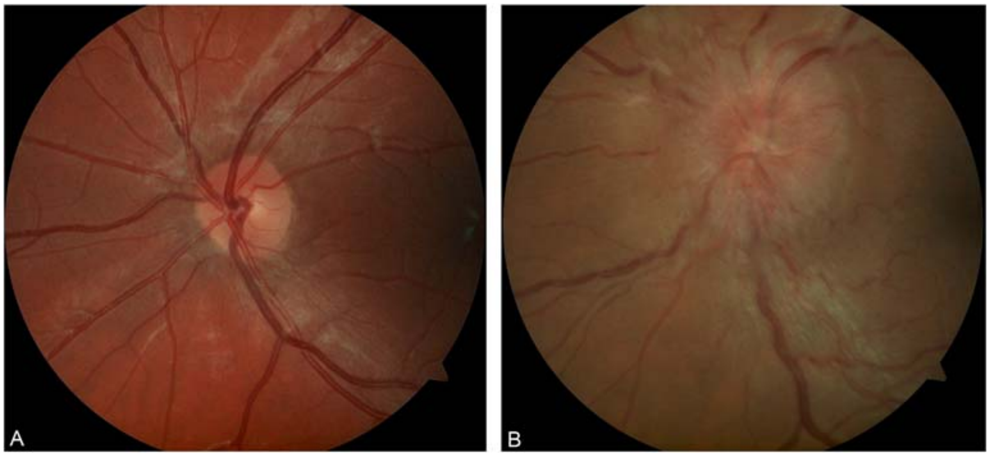


FIGURE 24-1 ■ *A*, Normal optic nerve. Note clearly visible vessels coursing over the disc edge, small central disc depression of the physiologic cup, and visible nerve fiber layer, especially in the superior and inferior arcades. *B*, Disc edema. Note obscurations of vessels coursing over the disc and swollen peripapillary nerve fiber layer causing disc elevation.

dysfunction. Bilateral symmetric optic nerve dysfunction does not produce a relative afferent pupillary defect as there is no difference in light transmission in the optic nerve of each eye, although both pupils will react sluggishly.

INFLAMMATORY DEMYELINATING OPTIC NEURITIS

Optic neuritis may be idiopathic or associated with demyelinating disease, most commonly MS. The clinical course is characterized by a relatively sudden onset of typically unilateral visual loss. The condition worsens to a nadir over several days, and then recovery begins, typically within several weeks, independent of corticosteroid treatment (although intravenous corticosteroids given in a 3-day course followed by a 2-week oral prednisone course and taper is a frequently used therapy).[1] Visual acuity at nadir ranges from 20/20 to no light perception. Pain occurs in more than 90 percent of cases, and often worsens with eye movement. Although centrocecal scotomas are classically associated with demyelinating optic neuritis, other types of field defects (e.g., central, altitudinal, diffuse, paracentral, and arcuate) frequently occur.

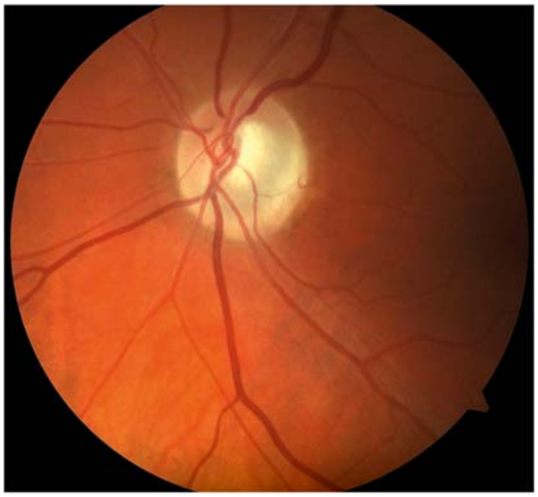


FIGURE 24-2 ■ Optic atrophy. Note disc pallor and lack of visible nerve fiber layer striations.

Demyelinating optic neuritis is retrobulbar in two-thirds of instances and the optic disc appears normal in the acute phase; the remainder of cases display mild disc edema acutely (“papillitis”). Magnetic resonance imaging (MRI) demonstrates contrast enhancement of the optic nerve in at least 90 percent of cases of demyelinating optic neuritis within the first several weeks, especially when fat-suppressed orbital sequences are obtained (Fig. 24-3).[2] Between 3 and 6 months after optic neuritis, optic atrophy becomes visible if there is nerve fiber loss, and visual evoked potentials may document delayed latencies. Not all cases of optic neuritis result in such optic atrophy.

While the overall prognosis of visual recovery from optic neuritis is good, it is common for many patients to have residual deficits ranging from mildly reduced contrast sensitivity to more significantly reduced acuity. The Optic Neuritis Treatment Trial followed patients with optic neuritis longitudinally and found that 72 percent of subjects had recovered visual acuity to at least 20/20, and 85 percent had acuity of at least 20/25 at 15 years after onset. If the initial visual acuity was limited to counting fingers or worse, there was a decreased chance of 20/20 (49%) or 20/25 (63%) visual recovery at 15 years. There was only a weak correlation between the severity of visual loss at baseline and recovery of vision in patients with an initial visual acuity between 20/20 and 20/200.

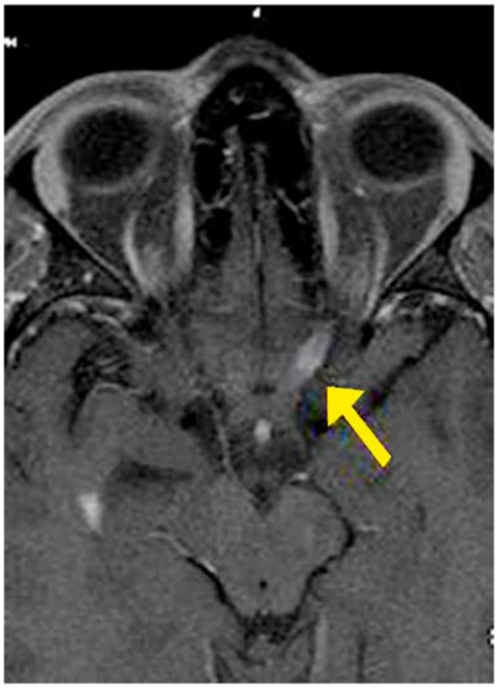


FIGURE 24-3 ■ Axial T1-weighted magnetic resonance imaging demonstrating gadolinium enhancement of the left retrobulbar portion of the optic nerve *(arrow)*.

The baseline brain MRI predicts the risk of developing MS in the decades following optic neuritis, and accordingly is an important test following a first attack of optic neuritis. The number of T2-weighted hyperintensities at least 3 mm in size on baseline MRI reflects the likelihood that a patient with optic neuritis will develop clinically definite MS as defined by a second subsequent relapse. A normal baseline MRI is associated with a 25 percent chance of developing MS in 15 years. The presence of just one lesion increases the 15-year cumulative probability of MS to 60 percent, while three or more lesions on the baseline brain MRI increase the likelihood to approximately 80 percent.[3] Optic nerve enhancement itself is not counted as a lesion. The overall risk of developing MS within 15 years after optic neuritis is 50 percent, independent of MRI findings, a figure that can be used to counsel those patients who cannot obtain an MRI. The majority of patients developing MS do so within the first 5 years. MRI characteristics also predict future disability in patients with optic neuritis. Spinal cord and infratentorial lesions are associated with a higher future disability.

NEUROMYELITIS OPTICA

NMO is an antibody-mediated inflammatory disease of the central nervous system (CNS) with a predilection for the optic nerves, spinal cord, and certain brain regions. While NMO was previously considered a variant of MS, it is now known to have distinct clinical, pathologic, and immunologic features. AQP4-IgG, a pathogenic antibody against aquaporin-4 (AQP4), has been shown to have high specificity to delineate NMO from presentations consistent with MS. More recently, a subset of patients with an NMO phenotype has been found to have autoantibodies targeting myelin oligodendrocyte glycoprotein.

Optic neuritis from NMO is often bilateral and frequently results in severe vision loss.[4] MRI features of NMO include involvement of greater than half the length of the optic nerve and involvement of the chiasm (Fig. 24-4). NMO-related optic neuritis is associated with greater retinal nerve fiber layer loss than MS, which can be measured by optical coherence tomography (Fig. 24-5).

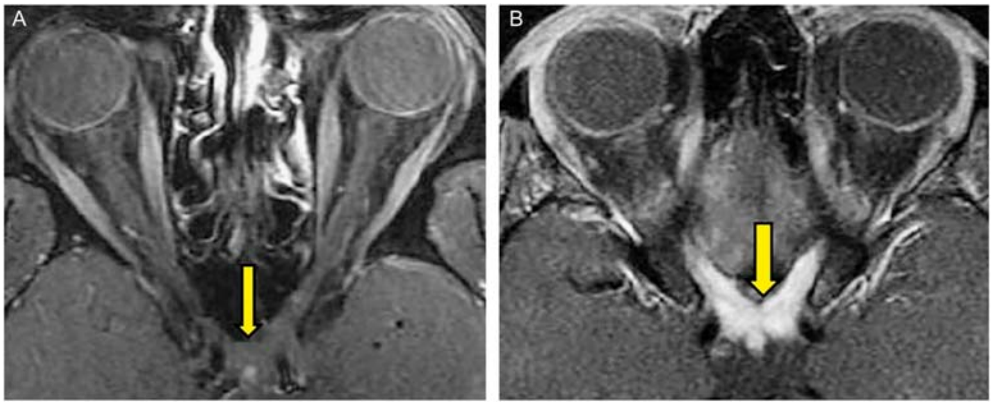
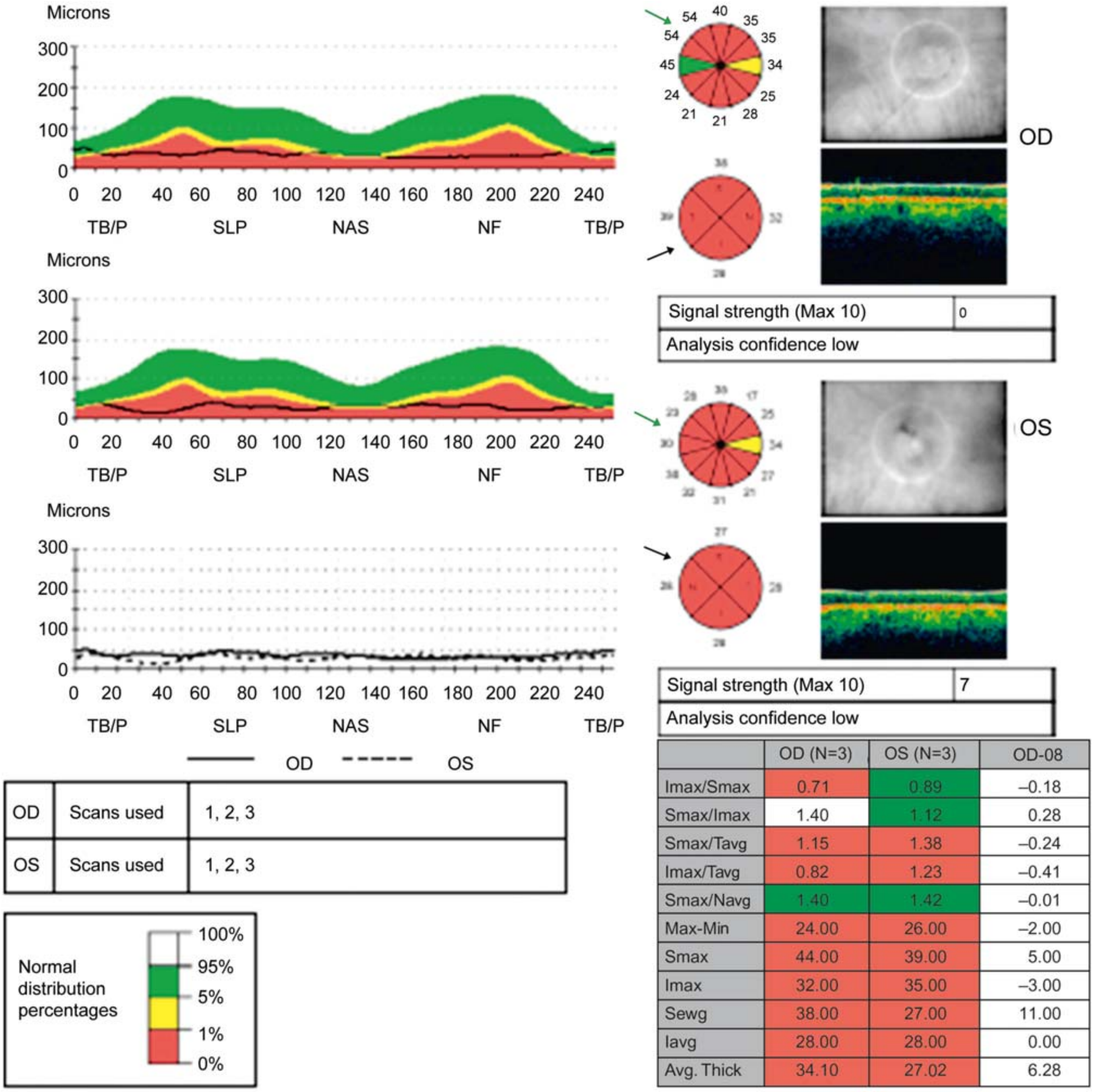


FIGURE 24-4 ■ Axial T1-weighted gadolinium-enhanced brain MRI at the level of the optic chiasm. *A*, Normal optic chiasm *(arrow)* does not enhance. *B*, An acute attack of neuromyelitis optica resulting in abnormal enhancement of the optic chiasm *(arrow)*.



OD	Scans used	1, 2, 3
OS	Scans used	1, 2, 3

Signal strength (Max 10)	0
Analysis confidence low	

Signal strength (Max 10)	7
Analysis confidence low	

	OD (N=3)	OS (N=3)	OD-08
Imax/Smax	0.71	0.89	–0.18
Smax/Imax	1.40	1.12	0.28
Smax/Tavg	1.15	1.38	–0.24
Imax/Tavg	0.82	1.23	–0.41
Smax/Navg	1.40	1.42	–0.01
Max-Min	24.00	26.00	–2.00
Smax	44.00	39.00	5.00
Imax	32.00	35.00	–3.00
Sewg	38.00	27.00	11.00
Iavg	28.00	28.00	0.00
Avg. Thick	34.10	27.02	6.28

FIGURE 24-5 ■ Optical coherence tomography demonstrating severe optic atrophy. Note sector *(green arrow)* and quadrant *(black arrow)* maps depicting dramatic nerve fiber layer (RNFL) loss in all quadrants. The average RNFL values of 34.1 μm (OD) and 27.02 μm (OS) indicate extreme optic atrophy (normal average RNFL ~104 μm).

Early treatment of NMO-associated optic neuritis with high-dose corticosteroids is associated with better visual outcomes and preservation of retinal nerve fiber layer. In cases where corticosteroids are ineffective or only transiently helpful, plasma exchange can be utilized; the effectiveness may depend on how early treatment is initiated.[5] Consequently, it is imperative to attempt to distinguish MS from NMO in the acute stage; bilaterality, severe visual acuity loss at onset, and recurrent visual decline following corticosteroid treatment are factors suggestive of NMO.

ISCHEMIC OPTIC NEUROPATHY

Ischemic optic neuropathy presents with acute visual loss due to impaired circulation to the optic disc or

TABLE 24-3 ■ Neuro-Ophthalmologic Disorders due to Ischemic Disease

Category	Funduscopic Features	Systemic Associations
Nonarteritic anterior ischemic optic neuropathy (NAION)	Generalized or sectoral disc edema, flame-shaped peripapillary hemorrhages, disc-at-risk in opposite eye	Diabetes, nocturnal hypotension, antihypertensive medications, sleep apnea
Nonarteritic posterior ischemic optic neuropathy	Normal in acute stage. May result in disc atrophy chronically	Severe systemic hypotension or anemia, sepsis
Arteritic ischemic optic neuropathy	Papilledema, evidence of choroidal ischemia, infarction in distribution of cilio-retinal artery, if present	Giant-cell arteritis, polymyalgia rheumatica, thrombocytosis, inflammatory aortitis
Diabetic papillopathy	Similar in appearance to NAION, but severity of fundus appearance may be out of proportion to relative sparing of visual function	Diabetes mellitus, diabetic retinopathy
Central retinal artery occlusion	Normal optic disc, but with generalized retinal edema with cherry-red macular spot	Carotid atherosclerosis, hypertension, tobacco use, hyperhomocysteinemia
Branch retinal artery occlusion	Normal optic disc with focal area of retinal edema, sometimes associated with a visible occlusive plaque	Carotid atherosclerosis, hypertension, tobacco use

retrobulbar optic nerve. It may be divided into arteritic (e.g., giant-cell arteritis) and nonarteritic varieties (Table 24-3). Nonarteritic anterior ischemic optic neuropathy (NAION) is always associated with disc edema acutely; the pathophysiologic mechanism of cell death is presumed to be mainly ischemia from impaired perfusion supplied by the network of short posterior ciliary arteries. Individuals with a crowded optic disc (small cup-to-disc ratio) are predisposed to developing NAION. It is believed that an episode of hypoperfusion to the optic disc can invoke a cycle whereby local ischemia gives rise to swelling of the crowded optic disc, which further compromises the circulation and leads to further swelling.

NAION typically presents with sudden, painless, unilateral vision loss, often with an altitudinal visual field defect (Fig. 24-6). Acutely disc edema may be focal or diffuse. Because the affected optic disc is swollen, the characteristic risk factor of a crowded optic disc is best observed in the opposite eye in the acute phase. Treatment for NAION is limited—systemic high-dose corticosteroids, intravitreal bevacizumab, and optic nerve decompression surgery are not effective. The risk to the opposite eye is approximately 15 percent over the next several years, and efforts should be made to address vascular risk factors such as hypertension, hyperlipidemia, and tobacco abuse. In addition, it is important to take measures to avoid nocturnal hypotension and treat obstructive sleep apnea if it is present.

Giant-cell arteritis (arteritic anterior ischemic optic neuropathy) is a neuro-ophthalmic emergency which may cause ischemia to the eye and optic nerve, leading to permanent visual loss. In addition, it can affect extraocular muscles and present with diplopia. Systemic symptoms such as jaw claudication, headache, scalp tenderness, fever, anorexia, weight loss, or polymyalgia rheumatica can be important clues to the diagnosis. Laboratory abnormalities include elevation of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as well as thrombocytosis; a normal ESR may be present in up to one-third of patients, but ESR and CRP together have a combined sensitivity of 99 percent.[6] Immediate treatment with corticosteroids is indicated when giant-cell arteritis is suspected and should be initiated even before biopsy, as histopathologic findings will persist for some time following corticosteroid exposure. For patients with difficulty weaning the dose of corticosteroids, tocilizumab has emerged as an effective

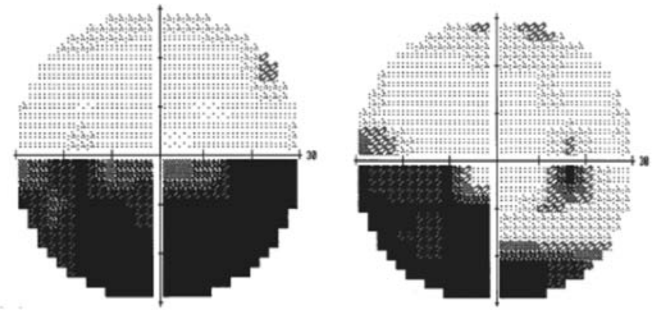


FIGURE 24-6 ■ Bilateral visual field defects in sequential nonarteritic anterior ischemic optic neuropathy. The right eye demonstrates an inferior arcuate defect with "nasal step" while the left eye reveals a denser inferior field defect.

immunotherapy targeting the IL6 receptor.[7] Temporal artery biopsy often demonstrates characteristic giant cells, noninfectious granulomas, inflammatory infiltrates, and interruption of the internal elastic lamina, although the phenomenon of skip lesions accounts for some biopsy-negative cases.

Posterior ischemic optic neuropathy is extremely rare and usually follows profound hypotension as a complication of surgery (especially prolonged spinal surgeries in the prone position), an episode of severe anemia, or as a result of giant-cell arteritis. Because the responsible lesion occurs distal to the lamina cribrosa of the optic nerve, the disc is not swollen (thus "posterior").

COMPRESSIVE OPTIC NEUROPATHY

Compressive optic neuropathies are usually painless (unless other cranial nerves are affected) and subacutely progressive (Table 24-4). When the lesion is intraorbital, associated features may include proptosis and optic disc swelling. Diplopia may be present, owing to restricted extraocular muscles or ocular motor nerve involvement. In contrast, retro-orbital lesions such as pituitary macroadenoma or intracranial meningioma cause visual loss and progressive optic disc pallor, but not optic disc edema. MRI including fat-saturated postgadolinium images is often the diagnostic tool of choice and coronal sequences are particularly helpful to delineate the relevant anatomy (Fig. 24-7).

TABLE 24-4 ■ Compressive Optic Neuropathy Locations and Etiology

Orbit	Sellar Region
Optic nerve sheath meningioma	Pituitary adenoma
Orbital metastases	Craniopharyngioma
Graves ophthalmopathy	Meningioma
Idiopathic orbital inflammatory pseudotumor	Internal carotid aneurysm
Primary bone lesions (e.g., fibrous dysplasia, Paget disease)	Histiocytosis
Orbital fracture or hemorrhage	

GENETIC OPTIC NEUROPATHY

While several inherited optic neuropathies have a chronic, insidious presentation, the main inherited optic neuropathy with an acute presentation is Leber hereditary optic neuropathy (LHON). LHON is a maternally inherited mitochondrial optic neuropathy that is phenotypically expressed most commonly in younger males. LHON typically produces bilateral, sequential, painless optic neuropathy with severe central scotomas causing profoundly reduced acuity. Acutely, the disc may appear erythematous with telangiectactic vessels, but no true disc edema is present. Genetic testing is commercially available for the three mitochondrial mutations that cause over 90 percent of cases. There is currently no proven

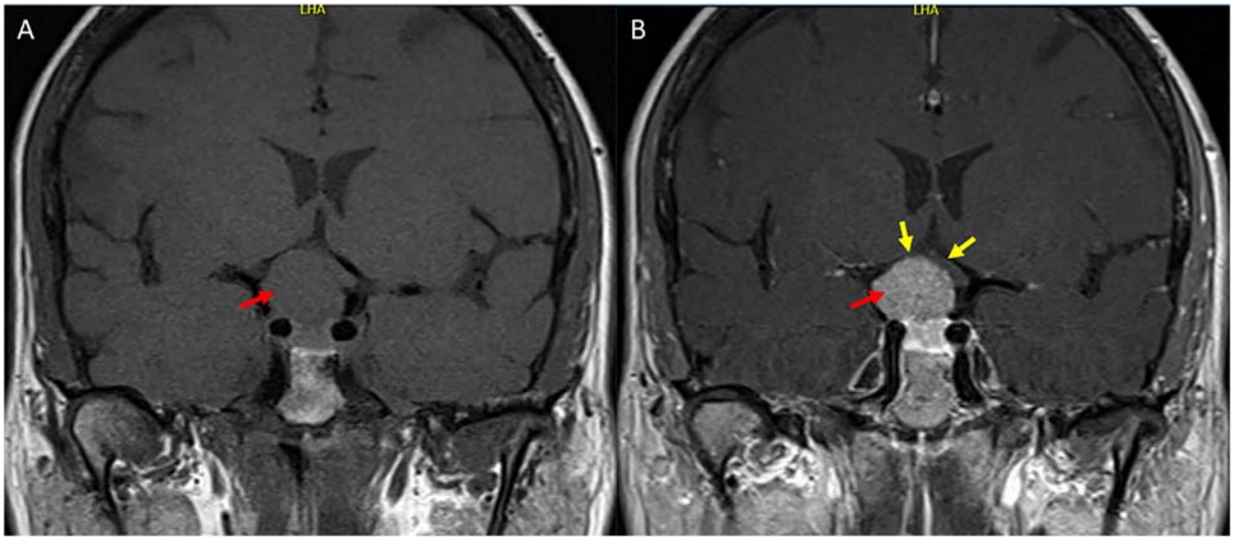


FIGURE 24-7 ■ Compressive optic neuropathy due to meningioma. Coronal T1-weighted MRI without (*A*) and with (*B*) gadolinium contrast shows a homogeneously enhancing lesion *(red arrows)* in the region of the pituitary sella compressing the optic nerves *(yellow arrows)* and chiasm inferiorly.

therapy; idebenone did not meet its primary endpoint of recovery of visual acuity in a randomized clinical trial but showed some promise when secondary endpoints were examined.[8] Gene therapy delivered by intravitreal injection is currently being evaluated in clinical trials.

PAPILLEDEMA

The term papilledema is meant to specifically refer to optic disc edema caused by elevated intracranial pressure (ICP), in contrast to the broader term optic disc edema, which also encompasses causes such as local ischemic, infiltrative, and inflammatory causes of optic neuropathy. Papilledema is nearly always bilateral, but can be asymmetric. It can range in appearance from mild to severe, described by using the Frisén scale (Fig. 24-8; Table 24-5). Peripapillary hemorrhages can be seen acutely but generally resolve once papilledema becomes chronic. Patients with papilledema often report other symptoms of elevated ICP, including headache, diplopia related to abducens neuropathy, and transient visual obscurations. In contrast to the significant central visual loss that can accompany other intrinsic causes of optic disc edema, the visual loss caused by papilledema often spares the central visual field. Visual loss caused by papilledema often starts with an enlarging blind spot and progresses to arcuate nerve fiber layer defects that may advance toward central visual loss when particularly severe. The most common causes of papilledema are listed in Table 24-6.

TABLE 24-5 ■ Frisén Scale for Rating Papilledema

Frisen Grade	Funduscopic Features
0	Normal except for mild blurring of the nasal and temporal disc
1	C-shaped peripapillary gray halo sparing temporal quadrant
2	360-degree gray peripapillary halo, nasal elevation
3	Obscuration of ≥1 major vessel segment at disc border, 360-degree elevation
4	Total obscuration of a major vessel on the disc
5	Partial obscuration of all vessels on the disc

Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension (IIH), or pseudotumor cerebri, is most characteristically a syndrome of obese females of childbearing age. Pediatric IIH is distinct in that the predisposition for obesity and female sex does not apply. The clinical characteristics of IIH include headache, pulsatile tinnitus, transient visual obscurations, and diplopia related to abducens nerve palsy.[9] Patients with IIH may have variable Frisén grades of optic disc edema. The pathophysiology of IIH is not fully understood, but vitamin A metabolism, endocrine-secreting adipose tissue, and cerebral venous dysregulation are all proposed possibilities. An emerging hypothesis is that cerebral venous sinus stenosis may be an important factor

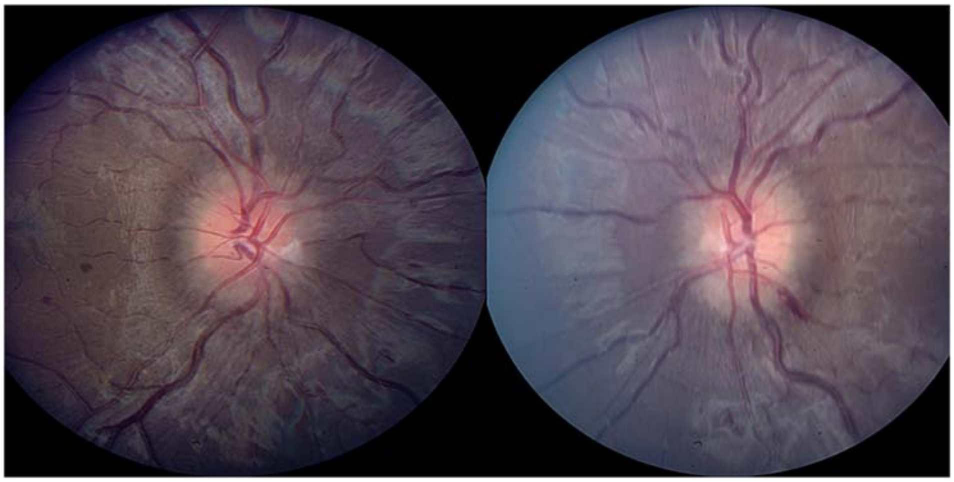


FIGURE 24-8 ■ Fundus photos showing papilledema. Both eyes are affected, as is typical. Features demonstrated include elevation of the retinal nerve layer, peripapillary flame-shaped hemorrhages, and engorgement of the retinal veins. Peripapillary blood vessels are obscured as they pass across the disc.

TABLE 24-6 ■ Causes of Increased Intracranial Pressure Resulting in Papilledema

Etiology	Concomitant Features
Space-occupying brain lesion	Subacutely worsening headache. Various neurologic defects depending on location
Meningoencephalitis	Meningismus, abnormal cerebrospinal fluid chemistries
Subarachnoid hemorrhage	Terson syndrome (intravitreal hemorrhage)
Cerebral edema	Vasogenic (due to loss of intracranial capillary integrity), cytotoxic (due to cell death, often as a result of ischemic stroke), or interstitial edema
Venous sinus thrombosis	Triad of seizure, encephalopathy, and headache is classic acute presentation
Cerebral aqueductal stenosis	May be asymptomatic until critical stenosis causes drowsiness and stupor
Superior vena cava syndrome	Dyspnea, face and arm swelling, Pemberton sign
Right heart failure	Peripheral edema, ascites, hepatomegaly
Sleep apnea	Hypertension, frequent napping, crowded oropharynx
Pulmonary hypertension	Parasternal heave, jugular venous distention, clubbing
Idiopathic intracranial hypertension	Obesity, female sex, childbearing age

contributing to the pathophysiology of this condition in some patients. Once the homeostatic mechanisms maintaining normal ICP have become impaired, elevated ICP can possibly create or worsen stenosis of the venous sinus, potentially causing a hemodynamically significant trans-stenotic pressure gradient. Higher pressure in the venous sinus may cause impaired function of the arachnoid villi that normally drain CSF into the venous sinuses, thereby perpetuating the cycle of events leading to elevated ICP.

The diagnostic evaluation of IIH requires brain imaging to exclude other etiologies of papilledema including venous sinus thrombosis and mass lesions; this is best accomplished with MRI and MRV. Radiologic features of IIH that are supportive of the diagnosis include an enlarged optic nerve sheath, optic nerve tortuosity, protrusion of the optic nerve head, an empty sella, and concavity or flattening of the posterior globes (Fig. 24-9).

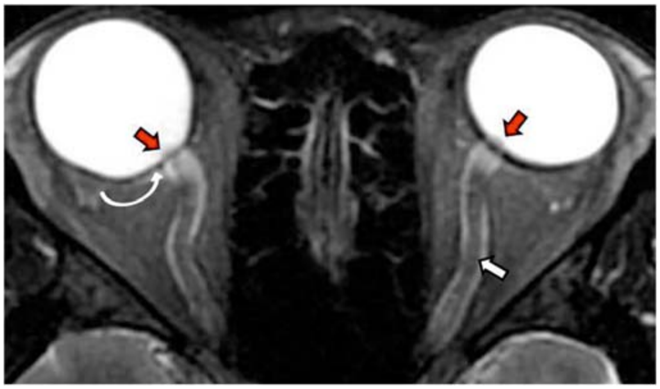


FIGURE 24-9 ■ Axial T2-weighted orbital MRI from a patient with idiopathic intracranial hypertension showing bulging of the papilla *(red arrows)*, flattening of the posterior globe *(curved arrow)*, and intraorbital nerve tortuosity *(white arrow)*.

Initial treatment for IIH may include weight loss, low-salt diet, and pharmacotherapy with acetazolamide. In cases relating to predisposing factors such as obstructive sleep apnea, excess vitamin A intake, tetracycline and related compounds, or chronic anemia, the underlying cause must be addressed. When visual loss is severe and progressive despite medical management, surgical options include optic nerve sheath fenestration, lumboperitoneal or ventriculoperitoneal shunting, or stenting of a hemodynamically significant venous stenosis.

Retrochiasmal Vision Loss

Lesions affecting postchiasmal afferent nerve pathways generally produce homonymous visual field loss, referring to visual loss on the same side of the vertical meridian of the visual field of each eye. Unless there is concomitant involvement of the optic nerve or the field loss is bilateral, visual acuity is typically spared. The most common causes of homonymous visual field loss are stroke, followed by trauma and tumors.

Higher order visual areas are organized into a ventral visual stream involving the temporal lobe (the "what" pathway) that is concerned with object recognition, and a dorsal stream including the parietal lobe (the "where" pathway) involved with spatial processing and motion. Ventral pathway dysfunction may produce difficulty with object recognition (specifically face recognition), whereas dorsal pathway lesions are associated with impaired spatial attention. While a unilateral right parietal lesion causes a rightward bias of attention (i.e., left-sided neglect), bilateral parietal lesions cause profound spatial impairment referred to as Balint syndrome. Balint syndrome is characterized by simultanagnosia (difficulty recognizing multiple components of a visual stimulus or scene), optic ataxia (difficulty reaching under visual guidance), and ocular apraxia (difficulty making accurate saccadic eye movements to an intended target).

Neurodegenerative disorders that cause predominant visual deficits early in the clinical course include dementia with Lewy bodies and posterior cortical atrophy, which is typically characterized by Alzheimer disease pathology. The Heidenhain variant of Creutzfeldt–Jakob disease affects the occipital regions first and presents with progressive visual processing deficits quickly leading to profound dementia, myoclonus, and death.

EFFERENT VISUAL DISTURBANCES

Clinical Assessment

The history in patients with diplopia should concentrate on whether the disorder is binocular or monocular, the orientation of the images, and symptom modifiers. Monocular diplopia—diplopia that remains when one eye is closed—is generally related to ocular causes (e.g., corneal or lens opacity, refractive error), and is not neurologic in origin. It typically resolves with the pinhole test and should prompt ophthalmology referral. In contrast, binocular diplopia resolves with closure of either eye; it is related to misalignment of the eyes and is typically neurogenic in origin. The direction of misalignment and the pattern of misalignment in each position of gaze allow accurate localization. Other factors such as age, associated features (e.g., ptosis, pain), modifiers, and diurnal variation (e.g., fluctuations) guide the differential diagnosis as discussed below.

Ocular misalignment refers to any deviation of the visual axis of one eye compared to the other. Ocular alignment can be measured on examination in several ways. An imprecise method involves estimation of misalignment by displacement of the corneal light reflex (Hirschberg method). Light reflects from the same position on both corneas if the eyes are orthophoric, whereas the light is displaced from the center in one eye when misalignment exists; each millimeter of light reflex displacement equals approximately 7 to 10 degrees or 15 to 20 prism diopters.

The red Maddox rod is a simple method to quantify small amounts of ocular misalignment. The Maddox rod is composed of a series of parallel cylindrical grooves in a piece of red glass, mounted in a circular rim (the original consisted of a single cylindrical rod, hence the name). The device converts a light source into a red line perpendicular to the axis of the rod. The patient views a white light source with the left eye, while the Maddox rod is placed over the right eye. The position of the red line relative to the light source (seen by the left eye) indicates the presence and amount of misalignment. The red line can be made to appear vertically (to measure horizontal deviation from the light) or horizontally (to measure vertical deviation from the light), and prisms can be placed over the Maddox rod until the line intersects the light. If the red line appears to the left of the light, then an exotropia exists. If the line appears to the right of the light, an esotropia is present. If the line appears below the light, then a right hypertropia is present, and a red line perceived above the light indicates a left hypertropia. By convention, vertical misalignment is always quantified by the hypertropic eye.

To perform the alternate cover test, the patient fixates on a target such as a specific letter of the Snellen chart, while the examiner alternately covers one eye and then the other. This technique forces the patient to fixate with the uncovered eye, disrupting binocular fusion and unmasking an underlying misalignment of the two eyes. If the eyes are orthophoric (aligned with each other), then no corrective eye movement will be required to fixate on the target when the occluded eye is switched. If an eye moves down to fix the target immediately after it is uncovered, then a hypertropia exists on that side. An exotropia is identified by an eye that moves in toward the nose to fixate the target once it is uncovered. In contrast, an outward eye movement to fixate a target indicates an esotropia. Prisms of increasing strength can be placed over one eye to neutralize this shift and quantify the misalignment.

These alignment tests are repeated in the nine cardinal positions of gaze to discern the pattern of involvement. If the misalignment is roughly the same amount in different directions of gaze, it is considered *comitant*, and may be a congenital form of strabismus that is not due to an acquired neurologic lesion. In contrast, if the deviation varies in different directions of gaze, it is considered *incomitant*, and the pattern of misalignment can help localize the neurologic lesion responsible for the diplopia. An incomitant esodeviation greatest in horizontal gaze indicates lateral rectus weakness on that side, often due to a partial sixth nerve palsy. An incomitant exodeviation indicates medial rectus weakness, often due to partial third nerve palsy or internuclear ophthalmoplegia. An incomitant hyperdeviation that increases in contralateral gaze and with ipsilateral head tilt is the pattern of a fourth nerve palsy. A hyperdeviation in downgaze that switches to the opposite hyperdeviation in upgaze often suggests a partial third nerve palsy, owing to combined weakness of the inferior and superior rectus muscles of the same eye. A hyperdeviation that does not fit the pattern of a fourth nerve palsy or third nerve palsy often represents a skew deviation, which is a supranuclear disturbance of vertical alignment caused by a brainstem or cerebellar lesion. For any pattern of ocular misalignment, orbital processes and ocular myasthenia gravis may also need to be considered.

The motility examination also includes assessment of pursuit, saccades, ductions, and versions. Pursuit is tested with the patient following a target moving slowly (less than 20 degrees/sec). Saccades are rapid eye movements that bring fixation from one target immediately to another. Binocular movements in various directions are known as versions, while ductions refer to the movements of one eye while the other eye is covered.

It can be worthwhile to note a patient's head position. Patients with diplopia may adopt a head posture to avoid the position of diplopia. For example, patients with impaired abduction of one eye may turn the head toward the side of the palsy. Patients with trochlear nerve palsy may present with a contralateral head tilt and chin-down position to avoid gaze into the diplopic field.

Examination of the eyelids, pupils, and position of the globe also provide important clues to the diagnosis. Ptosis should be quantified through measurement of the height of the palpebral fissure in millimeters. Pupil size should be measured in light, in dark, and with reactivity. Proptosis can be measured in millimeters of anterior displacement of each eye from the lateral canthus.

Anatomic localization is always the first task for a neurologist. The site of lesions causing binocular diplopia may be supranuclear (e.g., skew deviation or vergence dysfunction), or involve the ocular motor nerve nuclei or infranuclear segments of cranial nerves III, IV, and VI, the internuclear segment (i.e., medial longitudinal fasciculus [internuclear ophthalmoplegia]), neuromuscular junction (e.g., myasthenia gravis), or muscle (e.g., trauma, thyroid eye disease, neoplasm). A first step in localization is to consider the most specific patterns of ocular misalignment related to the ocular motor nerves or their nuclei as well as supranuclear and internuclear lesions (Tables 24-7, 24-8, and 24-9). If the misalignment pattern does not

TABLE 24-7 ■ Limitation of Upgaze

Entity	Motility	Globe Position	Eyelid	Pupil
Thyroid eye disease	Gaze in all directions may be limited	Proptosis, increased resistance to retropulsion	Eyelid retraction with lagophthalmos	Usually normal; RAPD if ON present
Orbital myositis	Gaze in all directions may be limited	Proptosis, increased resistance to retropulsion	None	Usually normal
Blow-out fracture with muscle entrapment	Isolated limitation of upgaze	Enophthalmos	Normal	Normal
Myasthenia gravis	Gaze in all directions may be limited; intrasaccadic slowing characteristic	Normal	Ptosis may be present	Normal
Parinaud syndrome	Skew deviation may be present	Normal	Eyelid retraction without lagophthalmos	Normal
Progressive supranuclear palsy	Symmetric limitation of vertical movement	Normal	Normal	Normal
Chronic progressive external ophthalmoplegia	Eventually gaze in all directions is limited	Normal	Normal	Normal
Superior division cranial nerve III	Isolated limitation of upgaze	Normal	Ptosis	Normal

From Cockerham KP, Olmos A: Orbital and ocular manifestations of neurological disease. p. 483. In Aminoff MJ (ed): Neurology and General Medicine. 4th Ed. Elsevier Churchill Livingstone, Philadelphia, 2008, with permission.
ON, Optic neuropathy; RAPD, relative afferent pupillary defect.

TABLE 24-8 ■ Limitation of Medial Ocular Movement

Disorder	Motility	Globe Position	Eyelid	Pupil
Thyroid eye disease	Gaze in all directions may be limited	Proptosis, increased resistance to retropulsion	Retraction/ lagophthalmos	Usually normal; RAPD should be sought
Orbital myositis	Any or all muscles may be affected	Proptosis, increased resistance to retropulsion	Usually normal	Usually normal
Myasthenia gravis	Gaze in all or any direction may be limited. Fatigue is common	Normal	Ptosis especially with fatigue or sustained upgaze	Usually normal
Internuclear ophthalmoplegia	Limitation of medial gaze, abducting nystagmus	Normal	Normal	Normal
Partial CN III palsy	Limitation of medial gaze is usually associated with limitation of upgaze and ptosis; in a complete third nerve palsy, the eye is exotropic	Normal	Ptosis is present if the superior division of CN III is affected	Pupillary fibers travel with the inferior division of CN III; if affected, the pupil will be dilated and have a decreased reaction to light

From Cockerham KP, Olmos A: Orbital and ocular manifestations of neurological disease. p. 483. In Aminoff MJ (ed): Neurology and General Medicine. 4th Ed. Elsevier Churchill Livingstone, Philadelphia, 2008, with permission.
CN, Cranial nerve; RAPD, relative afferent pupillary defect.

TABLE 24-9 ■ Limitation of Lateral Ocular Movement

Disorder	Motility	Globe Position	Eyelid	Pupil
Thyroid eye disease	Gaze in all directions may be limited	Proptosis, increased resistance to retropulsion	Retraction/lagophthalmos	Usually normal; RAPD should be sought
Orbital myositis	Any or all muscles may be affected	Proptosis, increased resistance to retropulsion	Usually normal	Usually normal
Medial wall fracture with entrapment	Isolated limitation of lateral gaze	Normal or enophthalmos	Acute, edema and ecchymosis; chronic, normal	Usually normal
Myasthenia gravis	Gaze in all or any direction may be limited; fatigue is common; intrasaccadic delay is characteristic*	Normal	Ptosis especially with fatigue or sustained upgaze	Usually normal
Cancer (paraneoplastic)	Gaze in all directions may be limited	Normal	Usually normal; may resemble myasthenia gravis	Normal
Sixth nerve palsy	Slowed saccades; esotropia in primary gaze	Normal	Normal	Normal

From Cockerham KP, Olmos A: Orbital and ocular manifestations of neurological disease. p. 483. In Aminoff MJ (ed): Neurology and General Medicine. 4th Ed. Elsevier Churchill Livingstone, Philadelphia, 2008, with permission.
RAPD, Relative afferent pupillary defect.
*Intrasaccadic delay refers to a saccade that is initially of normal or brisk velocity but slows as the eye moves laterally due to the decreased number and efficacy of the acetylcholine receptors.

conform to these specific patterns, attention should be directed toward neuromuscular junction disease, myopathy, or multiple cranial nerve palsies (e.g., Miller Fisher syndrome, Wernicke encephalopathy). One important caveat is that even if the pattern fits that of an ocular motor nerve, nucleus, or internuclear ophthalmoplegia, mimics such as myasthenia gravis must still be considered.

Supranuclear Causes of Ocular Dysmotility

The supranuclear ocular motor system is principally concerned with coordinating the movements of both eyes together, and when injured, produces gaze preferences or palsies. The set of inputs to the ocular motor nuclei in the brainstem arrive from the cerebral hemispheres, cerebellum, and portions of the brainstem, together governing distinct classes of eye movements including saccades, pursuit, the vestibular ocular reflex, gaze-holding, fixation, optokinetic nystagmus, and vergence. The hallmark of a supranuclear eye movement abnormality is that intact eye movements can be demonstrated when volitional pathways are bypassed, such as with the oculocephalic reflex.

The frontal eye fields of the cerebral hemispheres generate volitional contralateral saccades, and cerebral hemispheric lesions affecting these regions therefore produce a gaze deviation toward the side of the lesion. Occasionally, with deep lesions affecting the basal ganglia, the gaze deviation is toward the side of the lesion (so called *wrong-way eyes*).[10] Parietal lesions can interfere with smooth pursuit eye movements following a target moving toward the side of the lesion.

Supranuclear networks also control vergence eye movements. Convergence insufficiency is a relatively common example of vergence dysfunction, characterized by a larger exophoria (with diplopia) at near than far distance.

Within the pons, the paramedian pontine reticular formation just rostral to the abducens (VI) nucleus houses horizontal burst neurons. Lesions in this region produce slow or absent ipsilesional saccades. Burst neurons facilitating vertical saccades reside within the rostral interstitial medial longitudinal fasciculus, which is situated in the dorsal midbrain rostral to the oculomotor nucleus; dysfunction of this region produces slow or absent vertical saccades.

A dorsal midbrain syndrome, which is referred to by the eponym Parinaud syndrome, causes a supranuclear vertical gaze palsy. In its complete form, it is also accompanied by light-near dissociation of the pupils, eyelid retraction, and convergence retraction nystagmus.

The vestibulocerebellum, vermis, and fastigial nuclei perform critical coordination and calibration functions for the ocular motor system. The flocculus and paraflocculus are involved in smooth pursuit, gaze holding, and calibration of the vestibular ocular reflex. The vermis and fastigial nuclei are involved in saccadic and pursuit control. The nodulus and uvula participate in modulation of the vestibular system.

Skew deviation is a supranuclear cause of vertical diplopia, in which the nuclear and infranuclear third and fourth nerves are functioning normally but the supranuclear inputs that maintain normal vertical ocular alignment are perturbed. The vertical misalignment with skew is usually comitant (the same in all positions of gaze). Some cases of skew deviation may be incomitant, but usually not conforming to the pattern of misalignment of a third or fourth nerve palsy. The “high–high low–low rule” can be used to generally localize a lesion causing skew deviation; with lesions above the level of the pontine vestibular decussation, the ipsilesional eye is often hypertropic, and with lesions below this decussation, the ipsilesional eye is usually hypotropic. The ocular tilt reaction is a special circumstance of skew deviation with the additional features of involuntary head tilt and torsion of both eyes.

Ocular Motor Nuclei and Nerves

The three ocular motor nerves, which together are responsible for controlling the six extraocular muscles of each eye, are the oculomotor (III), trochlear (IV), and abducens (VI) nerves. Lesions of these individual nerves in the brainstem have characteristic patterns of clinical deficits with highly localizing value.

OCULOMOTOR NERVE (III) PALSY

The third cranial nerve innervates the superior, inferior, and medial recti, inferior oblique, levator palpebrae, iris sphincter, and ciliary muscles, thus controlling adduction, extorsion, supraduction, most of infraduction, lid opening, and pupil miosis. The collection of nuclei lie in the midline of the dorsal midbrain and are composed of a complex arrangement of subnuclei. The oculomotor nerve fascicles travel ventrally, traversing the red nucleus, substantia nigra, and cerebral peduncle before entering the subarachnoid space within the interpeduncular fossa. Within the subarachnoid space, the nerve projects between the superior cerebellar and posterior cerebral arteries, adjacent to the posterior communicating artery. It has an important anatomic relationship to the uncus, rendering the nerve vulnerable to compression with uncal herniation. Within the cavernous sinus, the nerve resides within the superior wall and divides into a superior division (innervating the levator palpebrae and superior rectus) and inferior division (innervating all its other muscles) prior to passing through the superior orbital fissure.

Lesions of the oculomotor nucleus are uncommon, and are characterized by ipsilateral third nerve deficits accompanied by bilateral superior rectus involvement and bilateral ptosis, owing to the anatomy of the individual ocular motor complex subnuclei. Lesions of the midbrain, often related to ischemia, are usually accompanied by hemiataxia, tremor, or hemiparesis.

Complete unilateral oculomotor nerve palsy produces complete ptosis, a mid-position light-fixed pupil, and an inability to adduct, supraduct, or infraduct the eye. The eye may appear depressed and abducted ("down and out"), and patients report binocular oblique diplopia when the lid is elevated. Partial oculomotor palsies may spare some aspects of this function.

The key diagnostic consideration in a patient presenting with an acute isolated third nerve palsy is aneurysmal compression, most commonly related to the posterior communicating artery. Rupture or enlargement of such an aneurysm typically produces an acute, painful, pupil-involved ipsilateral oculomotor nerve palsy. Prompt diagnosis is critical in facilitating treatment and reducing mortality. In contrast to potentially life-threatening aneurysmal oculomotor nerve palsies, ischemic (i.e., microvascular, "diabetic") palsies are much more common and nearly always improve. Ischemic injury often presents with pain, which may be indistinguishable from aneurysmal pain. In most cases of microvasculopathic third nerve palsy, the pupil is spared. Ischemic oculomotor palsies nearly always improve, never demonstrate aberrant regeneration, and usually resolve within approximately 3 months. Most patients with ischemic oculomotor nerve palsies are older, with some combination of vascular risk factors such as diabetes, hypertension, hyperlipidemia, and tobacco abuse. Treatment of ischemic palsies is focused on symptomatic relief, exclusion of other causes, and ischemic risk-factor modification.

The "rule of the pupil" is helpful in the evaluation, but must be applied correctly: in the face of a *complete* motor paresis, a normal pupil effectively eliminates compressive pathophysiologies such as aneurysm. It is critical to remember, however, that the rule of the pupil cannot be applied to rule out compression for incomplete motor palsies; in these cases, compressive etiologies remain a consideration regardless whether the pupil is involved or spared, and appropriate imaging is required to evaluate for lesions such as an aneurysm. Because the pupillomotor fibers reside on the dorsomedial peripheral aspect of the oculomotor nerve, and microvascular ischemic palsies tend to infarct the center part of the nerve, sparing the pupil occurs in approximately 70 percent of ischemic palsies.[11] When anisocoria does occur in microvasculopathic third nerve palsy, the pupillary inequality is typically less than 1 mm.

Oculomotor palsy from uncal herniation is related to ICP gradients and is always attended, in short order, by other features such as hemiparesis, diminished consciousness, or visual field defects. This neurologic emergency requires prompt therapy directed at the underlying cause as well as the intracranial hypertension itself in order to avoid morbidity and mortality. Many other conditions can cause oculomotor nerve palsy including pituitary apoplexy, giant-cell arteritis, trauma, infection, and tumor.

Because the oculomotor nerve innervates several muscles, palsies can heal with aberrant regeneration (synkinesis). The presence of such regeneration implies disruption of the perineural sheath from compression or trauma, and never follows microvascular palsies. Common aberrancy patterns include lid elevation with eye adduction or depression, eye adduction with vertical movements, and pupillary constriction with eye movements.

TROCHLEAR NERVE (IV) PALSY

The nucleus of the trochlear nerve resides in the dorsal periaqueductal gray of the caudal midbrain ventral to the aqueduct and dorsal to the medial longitudinal fasciculus. The fascicles of the trochlear nerve cross and exit the brainstem dorsally, tracing a long subarachnoid course around the midbrain and then through the cavernous sinus in its lateral wall. The nerve then passes through the superior orbital fissure to innervate the superior oblique muscle, which primarily intorts the eye (depression of the adducted eye is a secondary action).

Trochlear nerve palsies produce ipsilateral hypertropia and excyclotorsion, resulting in binocular oblique diplopia in contralateral and downgaze. The patient usually adopts a chin-down and contralateral head-tilt posture to diminish object separation. Examination of ductions, pursuits, and saccades is typically normal. Alignment testing typically reveals a hypertropia that is worse on contralateral gaze and with ipsilateral head tilt. The presence of ocular torsion can be demonstrated when viewing a straight horizontal line in a position of diplopia; the two horizontal lines will appear to converge toward the ipsilateral side with a trochlear nerve palsy.

Trauma is the most common cause of CN IV palsy, probably related to the long subarachnoid course of the nerve around the midbrain. Most patients with traumatic or ischemic (microvascular) trochlear nerve palsies improve with time; vertical prism may be useful if improvement is incomplete.

Abducens Nerve (VI) Palsy

The nucleus of the sixth cranial nerve resides in the dorsal pons, ventral to the facial nerve colliculus and adjacent to the medial longitudinal fasciculus. The nucleus contains abducens neurons innervating the lateral rectus and also internuclear neurons that travel through the medial longitudinal fasciculus to innervate the contralateral medial rectus subnucleus and mediate conjugate horizontal gaze. The fascicles of the abducens nerve emanate ventrally to emerge at the pontomedullary junction before ascending the clivus to enter the cavernous sinus and the superior orbital fissure.

Abducens nerve lesions cause binocular horizontal diplopia with an esotropia in ipsilateral gaze. In partial abducens nerve palsies, abduction may be only minimally impaired; alternate cover or red Maddox rod testing will demonstrate an incomitant esotropia. Abducens nuclear lesions cause an ipsilateral conjugate gaze palsy, where the abduction deficit of the ipsilateral eye is accompanied by an adduction deficit of the contralateral eye.

Duane type I retraction syndrome is a congenital dysinnervation syndrome that may be mistaken for an abducens palsy. This syndrome results from hypoplasia of the abducens nucleus, producing decreased abduction; however, in contrast to abducens palsies, patients with Duane type I retraction syndrome demonstrate retraction of the globe with adduction (evidenced by palpebral fissure narrowing).

Multiple Ocular Motor Nerve Palsies

Multiple ocular motor palsies should be localized either anatomically (e.g., all related to cavernous sinus disease) or through pattern recognition (e.g., ophthalmoplegia, ataxia, and confusion related to Wernicke encephalopathy). Cavernous sinus lesions commonly produce multiple cranial neuropathies, and may be related to neoplasms (e.g., meningioma, pituitary adenoma, metastasis), vascular causes (e.g., aneurysm, thrombosis, or carotid-cavernous fistulas), or inflammatory conditions (e.g., Tolosa–Hunt syndrome).

Miller Fisher Syndrome

Miller Fisher syndrome is an inflammatory polyneuropathy producing the classic triad of ophthalmoplegia, areflexia, and ataxia. It shares some features with acute inflammatory demyelinating polyradiculoneuropathy (AIDP) including increased cerebrospinal fluid (CSF) protein concentration without pleocytosis. Anti-GQ1b antibodies are present in the serum of most patients with Miller Fisher syndrome. Symptoms typically spontaneously remit in 2 to 3 months, perhaps accelerated by intravenous immunoglobulin or plasma exchange therapy.

Internuclear Ophthalmoplegia

Internuclear ophthalmoplegia is related to dysfunction of the medial longitudinal fasciculus, serving to connect the abducens nucleus to the contralateral oculomotor nucleus, coordinating binocular horizontal eye movements. Lesions may be unilateral or bilateral and commonly result from demyelination (the prototypic cause of diplopia in MS) or ischemia from basilar perforators.

Patients may report frank binocular horizontal diplopia (or oblique if the internuclear ophthalmoplegia is associated with skew deviation), but otherwise may note “dizziness” or visual blurring, or are asymptomatic. Slow adduction of the ipsilateral eye is the essential element; incomplete adduction is only present in a minority of cases, emphasizing the need to examine rapid horizontal saccades to make the diagnosis. Abducting and vertical gaze-evoked nystagmus are common accompaniments. Most improve spontaneously, whether due to demyelination or ischemia; the prognosis is less favorable with larger lesions accompanied by other signs of brainstem dysfunction.

Neuromuscular Junction Dysfunction

The estimated prevalence of myasthenia gravis (MG) is around 15 to 20 per 100,000 population in the United States. It has a bimodal distribution, tending to occur in the third decade among women and the seventh decade among men. MG presents with ocular signs and symptoms in up to 70 percent of cases. The rate of conversion from pure ocular disease to generalized MG is approximately 50 percent, typically in the first 2 to 3 years following presentation.

Antibodies against the nicotinic postsynaptic acetylcholine receptor are present in the serum of approximately 90 percent of patients with generalized MG but only about 50 percent of those with purely ocular MG. Some patients without these antibodies harbor antibodies to other neuromuscular junction components, such as muscle-specific kinase (MuSK) and low-density lipoprotein receptor-related protein (LRP-4).

Classically, MG causes ptosis of one or both eyelids and diplopia, but there are numerous variations. Ptosis or diplopia may be absent or intermittent, especially early in the course of the disease. Diplopia may be vertical, horizontal, oblique, or torsional, depending on the extraocular muscle involvement. The orientation and degree of diplopic object separation often vary over time, providing an important clue to the diagnosis, especially in seronegative cases. Associated clinical features of generalized MG include dysarthria, dysphagia, facial and orbicularis oculi weakness, and proximal limb weakness.

MG can cause weakness in any pattern of extraocular muscles; weakness of the medial rectus muscle is relatively common, sometimes closely mimicking the pattern seen with internuclear ophthalmoplegia. Patients often have gaze fatigue (gradual onset of extraocular weakness while attempting to hold eccentric gaze). Fatigable ptosis with sustained upgaze is also diagnostically helpful. The Cogan lid twitch is a sensitive (but not completely specific) sign of MG that is elicited by having the patient look at a target in downgaze for a few seconds, then saccade back to the primary position. A Cogan eyelid twitch appears as a 1- to 2-mm drop of eyelid elevation immediately after return to the primary position.

The ice and rest tests may be useful in the evaluation of suspected MG. The ice test is performed by placing an ice pack over a ptotic eyelid for 1 to 2 minutes and noting whether this reduces ptosis; it is likely that at least part of the ice test effect involves rest, as it is common for ptosis of both eyelids to improve somewhat after application of ice to one eyelid.

Edrophonium (Tensilon), a short-acting acetylcholinesterase inhibitor, can be used to demonstrate transient improvement in ocular signs related to neuromuscular junction defects. Dramatic improvement in ptosis is diagnostically useful. However, the test has both false-positive and false-negative results, and potentially dangerous side effects including bradycardia. Due to these limitations, Tensilon testing is rarely performed.

Nerve stimulation studies and electromyography provide the most sensitive method of quantifying neuromuscular defects. A decremental response to repetitive stimulation of a motor nerve is seen with postsynaptic neuromuscular junction disorders such as MG but is rarely seen in the pure ocular form of the disease. Single-fiber electromyography demonstrates increased variability in timing of activation of individual fibers within the same motor unit, referred to as jitter, in over 90 percent of MG cases.

Thymoma is present in approximately 10 percent of patients with MG, while thymic hyperplasia is present in approximately 70 percent. Thymectomy is routinely considered in thymoma cases, and a large multicenter trial showed its efficacy in younger patients with generalized MG to reduce the long-term corticosteroid requirement to maintain symptom control.[12] The decision to perform thymectomy in patients with purely ocular MG is made on an individual basis depending on the medication requirements for adequate symptom control, general medical health of the patient, and patient input.

Cholinesterase inhibitors such as pyridostigmine started at 30 to 60 mg three times daily are usually the first-line therapy in patients with ocular MG because of their relatively rapid onset of action and tolerable side-effect profile; however, most patients will also require immunomodulatory medications such as prednisone. Prednisone can be started in low-dose regimens, escalating as required; a corticosteroid-sparing medication such as azathioprine or mycophenolate mofetil can be started if long-term corticosteroid therapy is required.

Mechanical Causes of Diplopia

The most common acquired causes of extraocular muscle dysfunction in adults are thyroid eye disease, orbital trauma, and neoplasm.

Thyroid eye disease may occur with hyper-, hypo-, or euthyroid states and usually runs a course independent of the underlying thyroid disease (see Chapter 18). Thyroid eye disease typically produces painless proptosis, restriction of extraocular muscles with diplopia, eyelid retraction, and variable orbital inflammatory features. Lid retraction commonly leads to dry eye and corneal irritation, prompting treatment with corneal lubrication.

The inferior and medial recti are the most commonly involved muscles (typically with sparing of the tendinous insertions), producing hypotropia and esotropia. In approximately 10 percent of cases, extraocular muscle enlargement may produce an orbital apex syndrome resulting in compressive optic neuropathy. The diagnosis of thyroid eye disease is clinical, with imaging confirmation being somewhat helpful.

Treatment begins with correction of any thyroid derangements. Corticosteroids are used when proptosis is severe. Selenium and teprotumumab have been shown to be efficacious. Cases complicated by compressive optic neuropathy typically require urgent orbital decompression. Once stability has been established, which often takes 6 to 12 months, an orbital decompression can be performed to alleviate significant proptosis if necessary; diplopia may be addressed with strabismus surgery; and finally eyelid surgery can be performed to address eyelid retraction.

Orbital trauma not infrequently causes diplopia, often in the form of extraocular muscle entrapment. Blow-out fractures of the orbital floor may produce inferior rectus entrapment, often requiring surgical repair.

Orbital neoplasms (e.g., lymphoma, metastasis) or sinus-related processes that extend into the orbit (e.g., infection, nasopharyngeal carcinoma, mucoceles) may also produce mechanical dysfunction of the extraocular muscles and diplopia.

Excellent orbital imaging is achievable with computerized tomography (CT) or MRI, and the choice depends on the individual case. The advantages of CT include speed, multiplanar capability with newer scanners, and excellent bone detail, while MRI advantages include superior soft tissue resolution, multiplanar capability, and the lack of ionizing radiation.

Nystagmus and Other Abnormal Eye Movements

Nystagmus refers to abnormal spontaneous rhythmic eye movements that must include a slow phase. Jerk nystagmus is characterized by a series of slow phases followed by fast phases, while pendular nystagmus has back-to-back slow phases. Although nystagmus by convention is named for the direction of the fast phase, it is the slow phase that informs the clinician more about the pathophysiology.

The primary symptom directly correlating with nystagmus is oscillopsia, defined as the illusion of environmental movement, although patients with infantile-onset nystagmus are often asymptomatic.

Examination should emphasize looking for stability of the eyes in the primary position with and without ocular fixation and in sustained lateral and vertical positions of gaze. Abnormal involuntary eye movements should be evaluated for the presence of slow and fast phases, directionality, presence in one or both eyes, and the influence of position of gaze, posture, or time. Peripheral vestibular nystagmus is best observed without patient fixation, which can suppress the abnormality. Frenzel lenses provide a highly magnified view of the eyes and prohibit patient viewing, but this can also be accomplished by observing rhythmic movements of the fundus while performing ophthalmoscopy and occluding the opposite eye. Video-oculographic recordings provide objective and quantifiable assessment of ocular oscillations. The key patterns of commonly encountered nystagmus include gaze-evoked, peripheral vestibular, central vestibular, see-saw, and congenital patterns.

GAZE-EVOKED NYSTAGMUS

Once the eyes have moved to an eccentric position, elastic forces of the orbit pull the eyes back toward midline. To maintain steady eccentric gaze, centers in the brainstem and cerebellum known as the *neural integrators* provide the correctly calibrated amount of continued input (referred to as the *step function*) to the relevant ocular motor nuclei. Direction-changing nystagmus results from dysfunction of the neural integrators. The eyes develop slow phases back toward the primary position and require a fast corrective phase to return to eccentric gaze; the slow phase is always toward primary position. The neural integrator for horizontal gaze includes the flocculus and nodulus of the cerebellum, the nucleus prepositus hypoglossi, and the medial vestibular nuclei for horizontal movements, and for vertical gaze includes the interstitial nucleus of Cajal.

While physiologic endgaze nystagmus is characterized by a few beats of symmetric jerk nystagmus at the extremes of horizontal gaze, pathologic gaze-evoked nystagmus is characterized by sustained nystagmus, asymmetry (e.g., present in right but not left gaze), and sometimes other features such as rebound nystagmus. Rebound nystagmus is demonstrated by holding lateral gaze for several seconds during which sustained gaze-evoked nystagmus occurs, then observing a reversal of the direction of nystagmus upon return to the primary position (e.g., gaze-evoked right-beating nystagmus in right gaze is followed by a few beats of left-beating nystagmus after return to the primary position). Pathologic gaze-evoked nystagmus typically localizes to the ipsilateral cerebellum or its connections. Medications including anticonvulsants and sedatives may produce symmetric sustained gaze-evoked nystagmus.

PERIPHERAL VESTIBULAR NYSTAGMUS

Peripheral vestibular nystagmus typically contains torsional and either horizontal or vertical waveforms, and can be partially suppressed with visual fixation. In acute vestibular neuritis with dysfunction of all three semicircular canals, the typical nystagmus is characterized by a slow phase with horizontal and torsional components toward the paretic vestibular side followed by corrective fast phases away from the paretic side. This nystagmus is not direction-changing with different directions of gaze; the fast phase of the nystagmus is always away from the paretic side. Peripheral vestibular nystagmus generally obeys Alexander law: nystagmus is more pronounced in gaze in the direction of the fast phase and less pronounced (or perhaps not present at all) in gaze in the opposite direction. Large cerebellopontine angle tumors may produce Brun nystagmus, which is the combination of ipsilesional gaze-evoked nystagmus and contralesional peripheral vestibular nystagmus.

Benign paroxysmal positional vertigo (BPPV) presents with multiple brief episodes of vertigo, unlike the acute continuous vestibular syndrome caused by conditions such as vestibular neuritis or posterior circulation stroke. BPPV usually results from a canalith dislodged unto the posterior semicircular canal (with afferent connections to the ipsilateral superior oblique and contralateral inferior rectus). The pathognomonic finding on the Dix—Hallpike maneuver, therefore, consists of an upbeating torsional nystagmus toward the affected ear when the head is placed with that side down.

CENTRAL VESTIBULAR NYSTAGMUS

Central vestibular nystagmus typically results from lesions of the vestibulocerebellum (i.e., flocculus, nodulus, and vermis) or associated connections within the brainstem. Etiologies include brainstem and cerebellar processes such as infarcts, demyelination, neurodegenerative disorders, toxins, neoplasms, or Chiari malformations. Downbeat is the most common direction of central vestibular nystagmus; it is accentuated by, or may only be present in, down and lateral gaze. Upbeating nystagmus is much less common than downbeat nystagmus, and is usually associated with lesions in the medulla or cerebellum often related to demyelination, ischemia, or nutritional deficiency (e.g., Wernicke encephalopathy). Unlike peripheral nystagmus, central vestibular nystagmus is not influenced by visual fixation. Some patients with central vestibular nystagmus may respond partially to medications such as clonazepam, baclofen, gabapentin, memantine, or 4-diaminopyridine.

Periodic alternating nystagmus is a rare horizontal jerk nystagmus that rhythmically oscillates in direction, amplitude, and frequency; for example, nystagmus with slow phases leftward that increase in amplitude and frequency over 45 to 90 seconds, then wane and are followed by the development of nystagmus with slow phases to the right with predictable periodicity. Periodic alternating nystagmus may be congenital or acquired, localizes to the cerebellar nodulus, and often is related to multiple sclerosis, cerebellar degeneration, Chiari malformation, infarct, or bilateral visual loss. It is important to recognize due to its localizing value, and it may respond to baclofen.

Pendular nystagmus is characterized by sequential slow phases in the horizontal, vertical, or torsional planes, often combined into elliptical waveforms. Acquired pendular nystagmus is most commonly related to multiple sclerosis. Oculopalatal myoclonus or tremor is a special circumstance of pendular nystagmus, with palatal myoclonus synchronous with the nystagmus. This syndrome develops months to years after a lesion within the Mollaret triangle (i.e., cerebellar dentate nuclei, red nucleus, through the central tegmental tract to the inferior olivary nucleus in the medulla) leading to hypertrophic degeneration of the inferior olives that can be appreciated on MRI.

SEE-SAW NYSTAGMUS

See-saw nystagmus is an unusual phenomenon characterized by dysconjugate oscillations with one eye elevating and intorting, while the contralateral eye depresses and extorts. See-saw nystagmus is often pendular, but may be jerk, and is more commonly acquired than congenital. It tends to be associated with parasellar lesions (e.g., craniopharyngioma) often accompanied by bitemporal hemianopia.

CONGENITAL NYSTAGMUS

Congenital nystagmus, or infantile nystagmus syndrome, typically appears in the first few months of life as conjugate horizontal nystagmus that remains horizontal even in vertical gaze. It may have a complex waveform with both slow-phase velocity-increasing jerk nystagmus as well as pendular movements in varying positions of gaze. Patients with congenital nystagmus often turn the head to place the eyes in a direction of gaze with the least nystagmus (i.e., the null position), and do not typically report oscillopsia. Visual acuity may be relatively preserved, or may be decreased from the congenital nystagmus itself or from associated afferent conditions such as optic nerve hypoplasia or ocular albinism.

Latent nystagmus, or fusional maldevelopment nystagmus syndrome, involves horizontal jerk nystagmus that appears under monocular viewing conditions with the slow phase toward the nasal field of the viewing eye; the slow phase reverses direction when occlusion is switched from one eye to the other. Latent nystagmus is always accompanied by esotropia.

Monocular "shimmering" nystagmus in childhood, with very-low-amplitude vertical or elliptical movements, can occur with the relatively benign condition known as spasmus nutans, or in the setting of anterior visual pathway glioma, thus requiring neuroimaging.

SACCADIC INTRUSIONS

Saccadic intrusions are composed entirely of fast phases that disrupt fixation, in contrast to nystagmus that has pathologic slow-phase eye movements. Saccadic intrusions can be categorized by their intersaccadic interval. Square-wave jerks are horizontal small-amplitude (<5 degrees) saccades separated by an intersaccadic interval of approximately 200 msec. Square-wave jerks are very common, and normal elderly patients may exhibit a few per minute; however, they indicate underlying pathology when they are more frequent or accompanied by other features such as extrapyramidal signs. Ocular flutter is a purely horizontal saccadic intrusion without an intersaccadic interval, while opsoclonus consists of multiplanar saccadic intrusions without an intersaccadic interval. These disorders typically result from paraneoplastic or postinfectious autoimmune conditions, and less commonly from multiple sclerosis, brainstem encephalitis, toxins, or severe metabolic derangements (e.g., hyperosmolar coma). Voluntary "nystagmus" resembles flutter, with rapid conjugate back-to-back horizontal saccades without an intersaccadic interval. Because there is no slow phase, these movements are not truly nystagmus. Individuals who can produce voluntary nystagmus can typically sustain it for no more than a few seconds, and often converge when inducing this movement.

OTHER OCULAR MOVEMENTS

Patients with superior oblique myokymia describe brief episodes of monocular oscillopsia due to very low-amplitude, high-frequency, paroxysmal torsional oscillations of the superior oblique muscle of one eye. Episodes typically last only seconds, but may recur numerous times throughout the day. If an episode occurs during examination, the movements are more easily observed with magnification, such as during slit-lamp biomicroscopy. The condition is benign and often responds to carbamazepine, baclofen, gabapentin, or topical β-blockers.

Oculomasticatory myorhythmia is a rare pendular, vergence oscillation that occurs in synchrony with contractions of the masticatory muscles; it is essentially pathognomonic of Whipple disease, a rare infection caused by *Tropheryma whipplei*, which may also produce fever, diarrhea, cognitive dysfunction, and arthralgias (see Chapter 13).

Coma is caused by lesions involving either the brainstem or cerebral hemispheres bilaterally, and the eye examination can assist in this differentiation. Slow conjugate roving horizontal eye movements generally indicate a structurally intact brainstem. Rare "ping-pong" gaze, consisting of alternating conjugate horizontal gaze every few seconds, most often occurs with a large acute pontine lesion, but can also occur with bilateral destructive lesions of the cerebral hemispheres.

Ocular bobbing is a rare but ominous sign consisting of rapid conjugate downward eye movements followed by a slow return to the primary position, usually accompanied by bilateral horizontal gaze palsies. Ocular bobbing indicates a destructive pontine lesion and very poor prognosis for neurologic recovery. Other variations of this type of eye movement abnormality are ocular dipping (slow downward movement followed by rapid return) and reverse bobbing (fast upward, then rapid return to primary), but these have less localizing or prognostic value.

THE PUPIL

Examination of the pupils provides helpful information in a variety of clinical contexts. In contrast to other evaluations of visual function such as of acuity, color discrimination, and visual fields, pupil testing is objective and can be performed even without patient cooperation.

Anatomy

The axons of retinal ganglion cells travel through the optic nerve and then through the optic chiasm, where just over 50 percent of the fibers decussate to the contralateral optic tract. Within the optic tract, some axons bypass the lateral geniculate body to enter the brachium of the superior colliculus and synapse in the pretectal nucleus. The pretectal nuclei send efferent projections to each other and to both Edinger–Westphal nuclei, which issue fibers that innervate the iris sphincter via the oculomotor nerve.

Pupil dilatation involves the sympathetic pathways, which begin with first-order neurons in the hypothalamus. Axons from these neurons traverse the brainstem to the thoracic cord level, where the second-order cell bodies reside. Axons from these neurons enter the paravertebral sympathetic chain, before coursing over the lung apex to the superior cervical ganglion, where the final third-order cell body originates. These third-order sympathetic axons ascend as a plexus surrounding the internal carotid artery to enter the cavernous sinus before passing through the superior orbital fissure into the orbit to innervate the iris dilator muscles.

Because the midbrain receives retinal input from each eye, afferent visual dysfunction does not produce a difference between the size of the pupils. For example, the unilateral optic nerve section does not produce anisocoria; the pupil will not exhibit a direct light reaction, but will react consensually to light stimulation of the opposite eye.

A relative afferent pupillary defect results from asymmetric light input and is elicited by the swinging flashlight test. With the patient viewing a distance object, the examiner shines a bright light alternately in each eye for 1 to 2 seconds. Normally, both pupils constrict when the light is swung from one eye to the other. A relative afferent pupillary defect exists if, instead, both pupils dilate each time the light is shined into one eye. This phenomenon occurs because the brain perceives less light when stimulating the impaired optic nerve compared to the amount of light perceived with stimulation of the normal optic nerve, and then the Edinger–Westphal nuclei appropriately cause dilation of both pupils. A relative afferent pupillary defect is a sensitive and objective indication of asymmetric optic nerve dysfunction and does not occur with functional visual loss, refractive error, media opacity, or mild retinopathies. The swinging flashlight test requires two eyes, but just one working pupil (the pupils are isocoric with afferent lesions, so viewing either pupil provides the same information).

The Near Response

The near response consists of convergence, pupillary miosis, and accommodation. If the examiner encounters a pupil with an impaired light reaction, the next step should be to assess the pupillary response to a near target, which is a more potent stimulus to cause pupillary constriction. Several conditions are characterized by light-near dissociation, most notably Parinaud dorsal midbrain syndrome, Adie tonic pupil (see later), Argyll Robertson pupils, and severe afferent visual loss. Argyll Robertson pupils are bilaterally small, irregular pupils with limited light response compared to a brisk near response and prompt dilatation to distance viewing. This pupil abnormality is most associated with neurosyphilis. Severe afferent visual loss from pregeniculate causes such as optic neuropathy or widespread retinopathy will also produce light-near dissociation, but the clinical picture is dominated by visual loss in this setting. Oculomotor nerve aberrancy with a pupil that constricts in attempted adduction also produces light-near dissociation, as can a widespread neuropathy with autonomic involvement (e.g., severe diabetic neuropathy).

Anisocoria

Anisocoria may have many causes ranging from benign to life-threatening. An approach emphasizing the pupil size and reaction in light and dark will help categorize possible causes.

PHYSIOLOGIC ANISOCORIA

Physiologic anisocoria is characterized by briskly reactive pupils that differ in size by less than 1 mm. Patients are asymptomatic, and, accordingly, old photographs may assist in dating the onset of the asymmetry. Physiologic anisocoria is present in 20 percent of the population and typically produces anisocoria that is equal in light and darkness or slightly greater in the dark with normally reactive pupils to light, darkness, and accommodation.[13]

TRANSIENT ANISOCORIA

Transient anisocoria is usually related to benign etiologies such as migraine. Ominous potential causes include aneurysm or uncal herniation, but are unlikely in the asymptomatic patient with a normal examination.

HORNER SYNDROME

Horner syndrome refers to sympathetic paresis causing miosis, ptosis, and anhidrosis, although the full triad is rarely present.

Sympathetic fibers from the hypothalamus descend through the brainstem, where they may be affected by a lateral medullary lesion (Wallenberg syndrome), and then descend into the spinal cord to the level of C8 to T1, where the second-order fibers begin. Radiculopathy may affect this segment of the nerve before it ascends the lung apex to reach the carotid artery, moving toward the superior cervical ganglion, the site of the third-order neuron. The third-order fibers ascend on the carotid artery (pupillomotor fibers via the internal carotid and vasomotor plus sudomotor fibers via the external carotid branches) into the cavernous sinus, and then traverse the superior orbital fissure with the first division of the trigeminal nerve into the orbit to innervate the pupil dilators and the Müller muscles of the eyelid.

Horner miosis is related to impaired dilatation, and accordingly the anisocoria is greatest in darkness. Slowed dilatation in darkness over the course of 15 to 40 seconds is quite suggestive of sympathetic paresis. The ptosis of Horner syndrome relates to impairment of the Müller muscles, which are small ancillary muscles that assist in lid opening. Upper-lid ptosis in Horner is typically only 1 to 2 mm, and lower-lid or "upside down" ptosis can be present. The anhidrosis in Horner syndrome varies with the site of the sympathetic lesion, including hemibody with lesions of the first-order neurons, hemiface with lesions of the second-order neurons, or just a small patch above the brow with lesions of the third-order neurons. Many Horner syndromes are incomplete; the miosis is the most recognizable and reliable feature to guide diagnosis.

When the clinical features of miosis and anisocoria are greater in darkness, and dilation lag and mild ptosis are somewhat ambiguous, pharmacologic studies may aid in the diagnosis. Cocaine instilled into the eye blocks norepinephrine reuptake, thus increasing norepinephrine's action at the synapse and producing pupil dilatation if the sympathetic chain is intact. In addition to mydriasis, cocaine causes lid retraction and blanching of the conjunctiva. Postcocaine anisocoria of 1 mm is specific for Horner syndrome as opposed to physiologic anisocoria.[14]

Apraclonidine testing has emerged as a convenient way to perform pharmacologic testing to identify Horner syndrome. It is an α_2-adrenergic agonist, but also has weak α_1 agonist properties. This α_1 activation is too weak to cause dilation of a normal pupil, but will dilate an iris dilator that shows denervation hypersensitivity, thus producing a reversal of the pre-existing anisocoria.[15] Ptosis associated with Horner syndrome often also temporarily resolves with apraclonidine testing. One caveat to bear in mind is that false-negative testing can occur with apraclonidine testing in the acute period after Horner syndrome develops. While apraclonidine is safe in adults, it has risks of causing respiratory depression in children, so cocaine pharmacologic testing is still used when necessary to confirm Horner syndrome in that population.

Distinguishing whether Horner syndrome is due to involvement of third-order neurons or to preganglionic (first- or second-order) neurons can be accomplished with the instillation of hydroxyamphetamine drops. This agent releases acetylcholine from intact third-order neurons; postinstillation increase in anisocoria of 1 mm generally indicates a Horner syndrome due to a lesion of third-order neurons. In general however, hydroxyamphetamine testing has insufficient specificity to be clinically valuable to direct additional diagnostic evaluation once Horner syndrome is diagnosed.

Localization of the lesion causing Horner syndrome can generally be accomplished based on other associated neurologic findings. Lesions of first-order neurons are always associated with other CNS features. Lesions of second-order neurons may be caused by lung lesions (Pancoast tumor) or tumors within the neck or mediastinum. Pain or cephalgia with a third-order Horner syndrome raises concern for carotid dissection or skull-base neoplasm, but can also be seen in association with trigeminal autonomic cephalgias, especially cluster headaches. In the case of isolated Horner syndrome without associated features to aid in localization, it is prudent to obtain imaging of the brain, vascular imaging of the neck, and imaging of the upper chest, in order to identify a structural cause. Approximately 50 percent of cases of isolated Horner syndrome remain idiopathic, without an identifiable underlying cause.

ANISOCORIA GREATER IN LIGHT WITH ABNORMAL PUPILLARY LIGHT REACTION

Mechanical disruption of the iris may produce a pupil that reacts poorly to light (and often dilates poorly to dark). Surgery is the most common mechanism that mechanically impairs the iris, but infection or inflammation with synechiae tethering the iris to the lens; trauma; and angle-closure glaucoma may also be responsible. Distorted pupil shape, a history of intraocular surgery, and poor reaction to mydriatic drops are all clues of a mechanical origin.

Angle-closure glaucoma is an important condition to recognize as it may lead to irreversible visual loss. In its most severe form, the pupil is mid-position and nonreactive to light, associated with a cloudy edematous cornea, conjunctival injection, and pain. Precipitating factors include darkness or mydriatic drops. The diagnosis is made clinically including documentation of elevated intraocular pressure, and treatment involves an urgent reduction in pressure by pharmacologic and then surgical means.

The parasympathetic fibers innervating the pupil sphincter travel with the oculomotor nerve; however, palsies of the third cranial nerve never cause isolated mydriasis as a general rule, and accompanying eye movement limitations or ptosis are almost always present.

Several pharmacologic agents may produce mydriasis if instilled in the eye, either intentionally or by accident. Both anticholinergics and sympathomimetics will produce mydriasis. Commonly encountered anticholinergic agents include atropine, scopolamine patches, inhalers, insecticides, and many plant sources (e.g., belladonna). These agents typically produce maximal mydriasis (around 9 mm) with no response to 1 percent pilocarpine drops. Sympathomimetics such as epinephrine, phenylephrine, hydroxyamphetamine, cocaine, decongestants, and adrenergic inhalers produce mydriasis with a dampened light response. These pupils retain some reactivity to 1 percent pilocarpine drops.

TONIC PUPIL

Tonic pupil results from an idiopathic parasympathetic lesion involving the ciliary ganglion or postganglionic short ciliary nerves within the orbit. Acutely, the pupil is dilated with partial paresis of accommodation and light reaction. This partial paresis produces sectoral palsy of the iris, with limited sections partially reacting; this phenomenon is best observed with the slit lamp. Patients may report photophobia and complain of blurring of vision when reading or looking at near objects. The muscle stretch reflexes in the legs may be depressed, constituting the Adie-Holmes syndrome. Some patients develop segmental anhidrosis (Ross syndrome). With time (at least 1 week), supersensitivity develops, and even dilute pilocarpine (0.1%) may produce pupillary miosis (a normal pupil has no response to this dilute preparation of pilocarpine). As the short ciliary nerves regenerate, they give rise to aberrant innervation of the iris sphincter subserving the near response, thus creating light-near dissociation. Once the pupil constricts to a near stimulus, dilatation occurs only very slowly on release of convergence. Over years, the Adie pupil tends to become the smaller pupil, but retains the light-near dissociation and tonic response to accommodation.

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SECTION

8

Hematologic and Neoplastic Disease

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CHAPTER

25

Neurologic Manifestations of Hematologic Disorders

J.D. SUSSMAN ■ G.A.B. DAVIES-JONES

ANEMIA

- Iron-Deficiency Anemia
- Vitamin B_{12} Deficiency
  - *Peripheral Neuropathy*
  - *Myelopathy*
  - *Encephalopathy*
  - *Optic Neuropathy*
  - *Disordered Eye Movements*
  - *Infantile Vitamin B_{12} Deficiency*
  - *Imerslund—Graesbeck Syndrome*
  - *Nitrous Oxide*
- Folate Deficiency
- Sickle Cell Disease
- Thalassemia
- Hereditary Spherocytosis
- Paroxysmal Nocturnal Hemoglobinuria
- Cold Agglutinin Disease
- Cryoglobulinemia
- Kernicterus

RARE NEUROLOGIC SYNDROMES AND RED CELL ABNORMALITIES

PROLIFERATIVE DISORDERS

- Leukemia
  - *Meningeal Leukemia*
  - *Localized Leukemic Deposits*
  - *Chloromas (Granulocytic Sarcoma or Extramedullary Myeloblastoma)*
  - *Intracranial Hemorrhage and Thrombosis*
  - *Cellular Hyperviscosity*
  - *Infections*
  - *Leukoencephalopathy and Other Encephalopathies*
- Myelomatosis
  - *Spinal Myeloma*
  - *Cranial Myeloma*
  - *Peripheral Neuropathy*
  - *Neurologic Effects of Metabolic Complications*
  - *Neurologic Complications of Immunodeficiency*
- Macroglobulinemia (Waldenström Disease)
- Light/Heavy-Chain Deposition Disease
- Paraproteinemias
- Lymphoma
  - *Spinal Cord and Meningeal Involvement*
  - *Intracranial Involvement*
  - *Paraneoplastic Syndromes and Other Neurologic Complications*
- Burkitt Lymphoma
- Primary CNS Lymphoma
- Intravascular Lymphoma
- Lymphomatoid Granulomatosis
- Polycythemia
- Cerebellar Hemangioblastoma
- Pseudopolycythemia
- Essential Thrombocythemia
- Myelofibrosis
- Eosinophilic Syndromes
- Hemophagocytic Lymphohistiocytosis
- Macrophage Activation Syndrome

NEUROLOGIC COMPLICATIONS OF THERAPIES FOR HEMATOLOGIC MALIGNANCIES

- Chimeric Antigen Receptor T-Cell Therapies
- Checkpoint Inhibitors

HEMORRHAGIC DISORDERS

- Hemophilia A
- von Willebrand Disease
- Hemophilia B: Factor IX Deficiency
- Other Clotting Factor Deficiencies
- Acquired Hemophilia A
- Hemorrhagic Disease of the Newborn
- Thrombocytopenia
- Disorders of Platelet Function
- Disseminated Intravascular Coagulation
- Thrombotic Thrombocytopenic Purpura
- Hemolytic-Uremic Syndrome
- Gaucher Disease
- Bleeding and the New Anticoagulants

COAGULATION DISORDERS

- Antiphospholipid Antibodies
- Hereditary Thrombophilia
  - *Antithrombin III Deficiency*
  - *Protein C Deficiency*
  - *Protein S Deficiency*
  - *Factor V Leiden (RQ506Q)*
  - *Prothrombin G:A 20210 Mutation*
- Hyperhomocysteinemia
- Factor VIII
- Interactions Between Inherited Thrombophilias
- Thrombophilic Disorders and Arterial Thrombosis
- Patent Foramen Ovale

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ANEMIA

Iron-Deficiency Anemia

Nonspecific neurologic symptoms of tiredness, fatigue, weakness, poor concentration, irritability, faintness, dizziness, tinnitus, and headache are commonly associated with anemia. Occasionally, more concrete neurologic syndromes arise, such as the association of both idiopathic intracranial hypertension and cerebral venous sinus thrombosis with iron-deficiency anemia. The intracranial hypertension may resolve and recur with resolution and recurrence of the iron-deficiency anemia. In some patients with iron-deficiency anemia, thrombocytosis may be so high that it suggests a myeloproliferative disorder. The increased platelet mass may result in transient ischemic attacks (TIAs) or cerebral infarction. Profound anemia, particularly when associated with thrombocytopenia, may produce a retinopathy with papilledema, cotton-wool exudates, flame-shaped hemorrhages, retinal edema, and even retinal detachment. Blindness is a rare but well-recognized complication of massive hemorrhage; swelling of the optic discs is followed within a few weeks by optic atrophy.

Focal neurologic signs may arise from severe anemia in conjunction with severe cerebral atherosclerosis; symptoms may resolve completely over hours as the hemoglobin is increased. Severe anemia may also produce signs and symptoms that mimic Guillain–Barré syndrome.

Transient erythroblastopenia of childhood may present with papilledema and transient hemiparesis.

Restless legs syndrome may also be associated with various forms of iron-deficiency anemia including that related to frequent blood donation. Diminished iron and iron storage protein is found in the substantia nigra in restless legs syndrome, even in the presence of normal serum levels of iron and ferritin. It is recommended that patients with ferritin levels less than 75 μg/L, receive iron supplementation with the goal of achieving a ferritin level exceeding 100 μg/L. Restless legs syndrome may be associated with genes involved in iron metabolism and a third of the population carries genetic or systemic factors making them susceptible to the syndrome when peripheral iron is reduced. Iron deficiency and a strong family history (present in 72%) are characteristic of childhood-onset restless legs syndrome.

The US Health, Aging and Body Composition (Health ABC) study identified an association between anemia and an increased 10-year risk of dementia. The precise relationship is unclear.

Vitamin B_{12} Deficiency

Vitamin B_{12} (cobalamin) is a water-soluble micronutrient that serves as a coenzyme for cytosolic methionine synthase and mitochondrial methylmalonyl-CoA mutase. Cellular deficiency of cobalamin results in elevated levels of the B_{12}-dependent metabolites, methylmalonic acid (MMA), and homocysteine. Serum vitamin B_{12} has limited diagnostic value as a stand-alone marker; low serum levels of vitamin B_{12} do not always represent deficiency, and severe functional deficiency has been identified in the presence of normal or even high levels of serum vitamin B_{12}. There are no well-defined cut-offs for deficiency—likely deficiency has been defined as a value of less than 148 pmol/L and possible deficiency as a value between 148 and 258 pmol/L. Falsely normal or elevated levels of vitamin B_{12} have been reported when high-titer intrinsic factor antibodies interfere with the competitive-binding luminescence assay. Falsely low levels have been associated with multiple myeloma, oral contraceptive use, folate deficiency, and pregnancy. MMA levels increase in the presence of cellular deficiency of biochemically active tissue vitamin B_{12}, often preceding reduced plasma cobalamin levels, such that elevated MMAs can be found in the presence of a serum cobalamin within the reference range. Elevated total serum homocysteine is a sensitive marker of cobalamin deficiency but may also be related to familial hyperhomocysteinemia, levodopa therapy, renal insufficiency, and folate deficiency.

Among elderly individuals with low vitamin B_{12} levels, 20 to 40 percent have normal homocysteine and MMA blood levels and therefore should not be considered deficient in vitamin B_{12}. Holotranscobalamin (metabolically active fraction of vitamin B_{12}) represents up to 20 percent of the total vitamin B_{12} present in serum. It has been suggested that it is more accurate in assessing the biologically active fraction of vitamin B_{12} in circulation than the serum B_{12} itself. It is not known whether and how holo-transcobalamin levels vary in patients with inborn errors of intracellular vitamin B_{12} metabolism.[1]

Vitamin B_{12} deficiency may be caused by Addisonian pernicious anemia (elevated intrinsic factor and parietal cell antibodies), vitamin B_{12} malabsorption syndromes (including gastric and ileal resections, terminal ileal removal for lower urinary tract reconstruction, blind loops, and infestation with fish tapeworm), and dietary deficiency, particularly in vegans. A range of medications such as metformin and proton-pump inhibitors may also transiently induce reversible cobalamin deficiency, as does nitrous oxide inhalation. Advanced-stage patients with Parkinson disease receiving continuous intraduodenal infusion of levodopa-containing intestinal gel develop peripheral neuropathies thought to arise from transient deficiency of vitamins B_6 and B_{12}.

Subclinical vitamin B_{12} deficiency rarely evolves into clinical deficiency and the need for its treatment has not been fully established in spite of its much higher prevalence than clinical B_{12} deficiency.

The neurologic complications of vitamin B_{12} deficiency may occur without appreciable alteration in the peripheral blood; erythropoiesis may even be normoblastic, notably when vitamin B_{12} deficiency coincides with iron-deficiency anemia. Elevated MMA and total homocysteine are useful in establishing the diagnosis.

Functional vitamin B_{12} deficiency is defined by elevated levels of the B_{12}-dependent metabolites, MMA, and/or homocysteine, despite normal serum vitamin B_{12} values. Failure of intracellular transport or metabolism of vitamin B_{12}, for example by mutations in the transcobalamin 2 gene, can lead to cellular B_{12} deficiency. Such patients may respond to high-dose injections of vitamin B_{12}.[2] Functional vitamin B_{12} deficiency is common in subjects with advanced malignancy and cancer-related neuropathic pain and may respond to vitamin B_{12} therapy.

Peripheral Neuropathy

Sensory symptoms of peripheral neuropathy may be identical to those of vitamin B_{12} myelopathy. Somatosensory evoked potentials become abnormal before changes develop in peripheral nerves. Electrophysiologic studies indicate that the length-dependent neuropathy is secondary to a dying-back type of axonal degeneration, and neuropathologic studies have demonstrated loss of large myelinated fibers in distal sensory nerves as well as axonal degeneration in teased-fiber preparations.

Myelopathy

Demyelination followed by axonal degeneration affects the most heavily myelinated fibers first, which may explain why lesions appear primarily in the posterior columns and then later in the lateral columns. Progression may be subacute or rapid.

Suspicion that a sensory neuropathy may be related to vitamin B_{12} deficiency should be raised by upper-limb onset or an associated Lhermitte phenomenon. Myelopathy is accompanied by early and severe impairment of proprioception and vibration sense, sometimes accompanied by motor signs of the neuropathy. A severe sensory ataxic spastic paraparesis may be the sole manifestation of the myelopathy. Bladder symptoms may occur later. Pseudoathetosis is rare but may be prominent. Magnetic resonance imaging (MRI) may reveal hyperintense T2 signal in the dorsal cervical cord. Similar changes may occur with copper deficiency that may also arise from malabsorption following upper gastrointestinal surgery.

Encephalopathy

Multiple foci or diffuse areas of demyelination occur with little evidence of glial cell proliferation or axonal degeneration. Symptoms include disorders of mood, mental slowing, poor memory, confusion, agitation, delusions, visual and auditory hallucinations, aggression, dysphasia, and incontinence.

Neuropsychiatric assessment in patients presenting to general physicians with vitamin B_{12} or folic acid deficiency identifies organic mental change of unspecified nature in around 25 percent of patients, and affective disorders in around 20 percent of patients. The response to vitamin B_{12} therapy is variable.

Optic Neuropathy

Optic neuropathy is rare and may be the presenting feature. Optic atrophy may ensue.

Disordered Eye Movements

Downbeat nystagmus, paralysis of upward gaze, and internuclear ophthalmoplegia have all been attributed to vitamin B_{12} deficiency and have responded to therapy.

INFANTILE VITAMIN B_{12} DEFICIENCY

Infantile vitamin B_{12} deficiency may result from maternal vitamin B_{12} deficiency causing encephalopathy, epilepsy, and microcephaly. Long-term cognitive impairment and developmental delay may ensue.

IMERSLUND–GRAESBECK SYNDROME

This is an autosomal recessive condition caused by a defect in the receptor of the vitamin B_{12}–intrinsic factor complex of the ileal enterocyte and resulting in megaloblastic anemia, proteinuria, and mild multiple neurologic abnormalities.

NITROUS OXIDE

Nitrous oxide, which is commonly used as a recreational drug, irreversibly binds to, oxidizes, inactivates, and depletes vitamin B_{12}. Prolonged use typically presents as subacute combined degeneration of the spinal cord, but other presentations include sensorimotor peripheral neuropathy with demyelinating features in the absence of clinical or imaging evidence of myelopathy. Recovery is variable.

Folate Deficiency

In adults, the neurologic manifestations of folate deficiency include impaired cognition, dementia, depression, peripheral neuropathy, and subacute combined degeneration of the spinal cord. Cerebral folate deficiency typically presents in early infancy with seizures, delayed motor and cognitive development, cerebellar ataxia, spasticity, and visual and hearing impairment. Juvenile and adult-onset cases also occur. Peripheral neuropathy caused by folate deficiency has been described in a few cases in the absence of thiamine and vitamin B_{12} deficiency and alcoholism. Subacute combined degeneration of the cord accompanying diet-induced folic acid deficiency may occur and improves after treatment with folic acid. A variety of folate transport and metabolic disorders have been described, and blocking antibodies against folate receptors have been found in the serum in 25 of 28 children with cerebral folate deficiency and in none of matched controls.

Sickle Cell Disease

The complications of sickle cell anemia (HbSS) or of sickle C disease (HbSC) arise from formation of sickle cells and from hemolysis, with free hemoglobin and other erythrocyte products scavenging nitric oxide. Sickle cells adhere to various receptors on vascular epithelium producing aggregates, activation of platelets, production of inflammatory cytokines, vasomotor dysfunction with vessel occlusion, and proliferative vasculopathy. Children with sickle cell disease have reduced levels of the majority of endothelial coagulation inhibitors, further enhancing the adhesive interactions between sickle cells and injured cell membranes and endothelial cells.

Sickling occurs when PO_2 is low. In the presence of circulatory stasis or reduced cardiac output, oxygen extraction is increased such that sickling is more likely to occur. In sickle cell trait, the severity of sickling depends on the amount of HbS; the percentage of HbS in sickle cell trait can vary from 25 to 45 percent. In circumstances of severe hypoxemia, even patients with sickle cell trait (HbSA) may develop symptoms.

One-quarter of patients with sickle cell disease have neurologic manifestations, with cerebral infarction being most common. Cerebral infarction on brain MRI in the absence of a history or physical findings of stroke occurs in 27 percent of patients before their sixth birthday, and 37 percent by their fourteenth birthday. Intracranial hemorrhage is much rarer; subarachnoid hemorrhage is the most common form and is usually aneurysmal in etiology. In children, hemorrhage tends to be primary and possibly related to vasculopathy leading to stenosis of large extracranial or intracranial vessels from fibrous proliferation of the intima. Moyamoya syndrome has been described in sickle cell disease and trait.

Less common neurologic features include cranial neuropathies, radiculopathy, ischemic mononeuropathy, radiculomyelopathy from vertebral collapse as a result of bone infarction, spinal cord infarction, hypopituitarism, ischemic optic neuropathy, TIAs, and seizures.

Hydroxyurea reduces the frequency of painful episodes by raising the level of HbF, reducing vaso-occlusive events and mortality, and is the accepted standard of care. Voxelotor, a hemoglobin oxygen-affinity modulator, inhibits hemoglobin S polymerization, increases hemoglobin oxygen affinity and reduced red cell sickling, hemolysis, and anemia, and is a promising and significant disease modifier.

Subcortical cerebral infarction and venous sinus thrombosis have also been described in sickle cell trait. Measurement of IQ in children with hemoglobin SS demonstrates modest reductions, suggesting diffuse brain injury.

Cerebrovascular complications are relatively uncommon in HbSC disease, but a proliferative retinopathy is described. Recurrent transient impairment of vision due to occlusion of major retinal vessels is an unusual manifestation of HbSS disease.

Thalassemia

Chronic anemias are associated with extramedullary hematopoiesis. There have been a few reports of spinal cord compression, most commonly in the middle to lower thoracic region. Surgical decompression plus radiotherapy is curative. Treatment with corticosteroids, blood transfusions, and local radiotherapy has also been successful. Transfusion to maintain the hemoglobin level above 12.5 g/dL may resolve minor compression of the spinal cord, with near-complete resolution of the extradural hematopoietic mass. Visual failure secondary to suprasellar extramedullary hematopoiesis in β-thalassemia has been described.

Severe forms of β-thalassemia, particularly following splenectomy, can be associated with hypercoagulability, with an increased risk of cerebral venous thrombosis. There is a reported association with moyamoya syndrome. Neurophysiologic evaluation demonstrates polyneuropathy in 39 percent, myopathy in 28 percent, and both in 17 percent of patients, correlating with iron overload.

Hereditary Spherocytosis

Hereditary spherocytosis has few neurologic sequelae. It is associated with a state of chronic anemia which results in a reduced cholesterol level and therefore a reduced rate of carotid occlusion and stroke. There have been reports of moyamoya syndrome in children with hereditary spherocytosis, and of anterior ischemic optic neuropathy in adults.

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria is a rare acquired hematopoietic stem-cell disorder arising from a range of mutations in the phosphatidylinositol glycan class A (*PIGA*) gene, resulting in a deficiency of a glycosyl phosphatidylinositol–anchored protein. It may occur de novo or in association with marrow hypoplasia, ranging from pancytopenia to aplastic anemia. It results in deficiency in the binding of several protective red cell membrane proteins and leads to hypersensitivity to complement. The disorder is characterized by intravascular hemolysis and manifested by episodes of hemoglobinuria and venous thrombosis. Hemolysis occurs throughout the day and is not paroxysmal, but hemoglobinuria is seen when the first concentrated urine is passed in the morning. The commonest manifestation is large-vessel venous thrombosis particularly in the brain and portal system. The spinal cord is not affected. An occasional patient suffers TIAs that have been attributed to the hypercoagulable state induced when excess thromboplastin is released from lysing red blood cells. Increased sensitivity of the red cells to lysis by complement stimulates platelet aggregation, leading to hypercoagulability. The hemoglobin released by hemolysis binds with circulating nitric oxide and inhibits the relaxation of smooth muscle, which results in abnormal tone of vascular smooth muscle, vasculopathy, and endothelial dysfunction. A neurologic cause of death is described in 10 percent of patients, including cerebral venous thrombosis, subarachnoid hemorrhage, and intracerebral hemorrhage. Moyamoya has been associated with paroxysmal nocturnal hemoglobinuria. The majority of patients without neurologic symptoms have brain MRI white matter abnormalities related to chronic ischemic small-vessel disease.

Eculizumab, a humanized monoclonal antibody that inhibits complement component C5, is an effective treatment, but allogeneic bone marrow transplantation is the only cure.

Cold Agglutinin Disease

Cold agglutinin disease is a form of autoimmune hemolytic anemia usually associated with IgM antibodies (rarely IgG and IgA cold-reactive autoantibodies) directed against erythrocytes with binding activity that increases as the temperature approaches

0°C. Cold-associated circulatory symptoms are very common. It is associated with a low-grade lymphoproliferative B-cell disorder in 90 percent of cases, but with a very low rate of developing overt lymphoma. Cold-induced circulatory symptoms with characteristic seasonal variations in anemia occur. The anemia is variable and usually not severe, though approximately 50 percent of patients are transfusion dependent at some time during the disease. Cold agglutinin–associated asymmetric sensory-motor neuropathy has been described as a feature of transformation to Waldenström macroglobulinemia.

Cryoglobulinemia

Cryoglobulins are serum proteins or protein complexes that undergo reversible precipitation at low temperatures. Three main types are recognized. Type I, most commonly monoclonal IgM or IgG, is seen in association with multiple myeloma, Waldenström macroglobulinemia, and other lymphoproliferative disorders. Type II consists of mixed immunoglobulin complexes in which the monoclonal antibody has specificity for polyclonal IgG and occurs in association with lymphoproliferative diseases, autoimmune disorders, and hepatitis. Type III cryoglobulin is composed of polyclonal immunoglobulin and is found in infections and autoimmune disorders. Neurologic complications are common in types II and III, with mononeuritis multiplex, peripheral symmetric sensorimotor axonal or demyelinating polyneuropathy, and small-fiber sensory neuropathy being the most common findings. More rarely, cerebral ischemia or vasculitis may occur.

Kernicterus

Kernicterus may be produced by any hemolytic process of sufficient severity in neonates, particularly in premature infants with physiologic jaundice. It is part of the spectrum of symptoms of acute bilirubin encephalopathy. In the developed world, an underlying cause is found in most patients. Glucose-6-phosphate dehydrogenase is a major source of protection from bilirubin-induced oxidative stress, and its deficiency syndrome leads to a high incidence of kernicterus. Whenever the serum unconjugated bilirubin level exceeds 20 mg/dL during the first few weeks of life, kernicterus may occur, though there is a poor correlation between bilirubin levels and disease severity. Unconjugated bilirubin is highly lipid soluble; it enters the brain and binds to neurons resulting in neuronal loss, demyelination, and gliosis, particularly in the basal ganglia and cerebellum. The neurologic features range from decreased alertness, hypotonia, and poor feeding to retrocollis, opisthotonos, and long-term sequelae. Chronic changes may evolve over a number of years, including the development of eye movement abnormalities, hearing loss, and extrapyramidal disorders (particularly athetosis and, less commonly, chorea). Cognitive function is relatively well preserved.

RARE NEUROLOGIC SYNDROMES AND RED CELL ABNORMALITIES

The term *neuroacanthocytosis* describes a number of conditions associated with abnormal erythrocyte membrane constituents, resulting in the formation of spiculated cells.

Pantothenate kinase–associated neurodegeneration, or neurodegeneration with brain iron accumulation type I (NBIA-1), is an autosomal recessive disorder in which classic forms are associated with *PANK2* mutations on chromosome 20. Patients are normal at birth but then develop acanthocytosis, dystonia, dysarthria, rigidity, occasional spasticity, cognitive impairment and dementia, pigmentary retinal degeneration, optic atrophy, and iron accumulation in the brain, particularly in the globus pallidus. MRI shows the "eye-of-the-tiger sign"—hyperintensity within the hypointense medial globus pallidus—but this sign may not be present in early cases. The classic form presents in the first decade, with progression and loss of independent ambulation within 15 years. Atypical forms develop in the second decade and progress slowly, with retained independent ambulation up to 40 years later. Intermediate forms are described. Early onset is associated with pigmentary retinopathy, whereas a later onset is associated with speech disorders and psychiatric features. Pantothenate kinase catalyzes the first committed step in the universal biosynthetic pathway leading to CoA and is located in the mitochondrial intermembrane space. Mutations in *PANK2* are also found in HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration).

Bassen–Kornzweig disease (neuroacanthocytosis with abetalipoproteinemia) is a recessively inherited syndrome characterized by acanthocytosis, retinitis pigmentosa, increasing cerebellar ataxia, peripheral neuropathy, steatorrhea, and complete or almost complete lack of serum β-lipoproteins, with onset during childhood. The microsomal triglyceride transfer protein (*MTTP*) gene is essential for synthesizing β-lipoproteins for the absorption and transport of fats and cholesterol. Mutations in the gene result in deficiency of fat-soluble vitamins, A, D, E, and K, though deficiency of vitamin E is the primary cause of the degeneration in spinocerebellar and dorsal columns of the spinal cord. Treatment with vitamins A and E as early as possible is helpful.

Chorea-acanthocytosis is an autosomal recessive disorder linked to the *VPS13A* gene on chromosome 9 which encodes chorein. The neurologic features commence between 25 and 45 years with behavioral change and obsessive-compulsive disorder, followed later by the development of progressive choreiform movements of the limbs, face, mouth, lips, and throat—lip and tongue biting is characteristic. Myopathy and neuropathy may occur. In addition, motor or vocal tics, dystonia, parkinsonism, progressive supranuclear palsy, and apraxia of eyelid opening have been described. Serum creatine kinase levels are elevated; serum lipoproteins are normal.

McLeod neuroacanthosis is an X-linked syndrome with absent expression of Kx erythrocyte antigens, weak expression of Kell glycoprotein antigens, and increased serum creatine kinase levels. A range of other features may include hemolytic anemia, myopathy, limb chorea, facial tics, lip and tongue biting, neuropathy, dystonia, seizures, psychiatric changes, cognitive impairment, and dilated cardiomyopathy.

Huntington disease-like syndrome (HDL2) is an autosomal dominant disorder found almost exclusively in people of African ancestry. It is characterized by a trinucleotide repeat in the junctophilin-3 gene. Acanthocytosis is a variable feature. There is striatal and cortical atrophy, as well as intranuclear protein aggregates. HDL2 is clinically and radiologically indistinguishable from Huntington disease, with typical juvenile and late-onset forms.

A progressive spinocerebellar syndrome and sideroblastic anemia occur together in an X-linked recessive mutation in the *ABCB7* gene that encodes the ATP-binding cassette subfamily B member 7, mitochondrial. It is a mitochondrial disorder caused by a mutation in the nuclear genome. Cerebellar ataxia and dysarthria develop by 1 year of age, with accompanying long-tract signs. The neurologic signs tend to be stable until the fifth decade, when slow progression may occur. Neuropathy and myopathy have been described in association with sideroblastic anemia.

Triosephosphate isomerase deficiency is a rare autosomal recessive metabolic disorder characterized by chronic hemolytic anemia, progressive neurologic dysfunction, and an increased susceptibility to infection. The neurologic features consist of a dystonic-dyskinetic syndrome with gross intention tremor and amyotrophy and hypotonia of the trunk and limbs, sometimes with corticospinal signs. There is electromyographic evidence of denervation with normal nerve conduction velocities, suggestive of anterior horn cell impairment. It has been suggested that low triosephosphate isomerase activity leads to a metabolic block in the glycolytic pathway and hence to an impairment of the cellular energy supply.

PROLIFERATIVE DISORDERS

Leukemia

Involvement of the central nervous system (CNS) is primarily due to infiltration with leukemic cells, but may occur as the result of hemorrhage, infection, drug- and radiation-induced neurotoxicity, electrolyte disturbance, and impairment of cerebral circulation from leukostasis.

MENINGEAL LEUKEMIA

The most common presenting symptoms are headaches, nausea, and vomiting, sometimes associated with lethargy and irritability, neck stiffness, drowsiness, coma, and convulsions. Diffuse meningeal infiltration impairs the circulation of CSF and can result in communicating hydrocephalus. Papilledema is the most common sign. The leukemic deposits may compress or infiltrate the cranial nerves or spinal nerve roots and spread between the nerve fibers.

The diagnosis of meningeal leukemia is confirmed on CSF examination in approximately 90 percent of cases. Flow cytometric analysis of CSF has the highest diagnostic yield. The CSF pressure is usually elevated and reduced glucose concentration may be found. In 10 percent of cases the CSF is normal and repeated CSF examinations may be required.

Acute myelomonocytic leukemia accompanied by pericentric inversion of chromosome 16 is a unique subtype associated with a high incidence of CNS involvement in the form of leptomeningeal deposits and granulocytic sarcoma (chloroma).

LOCALIZED LEUKEMIC DEPOSITS

Leukemic deposits may involve any part of the CNS (Figs. 25-1 and 25-2). The symptoms and signs are therefore numerous, varied, and depend on the extent and site of infiltration. Blindness may occur from infiltration of the optic nerve head or chiasm, and visual impairment from retinal infiltration. Bilateral serous macular detachment with visual blurring may be the presenting symptom of acute lymphoblastic leukemia. Mental nerve involvement that produces sensory impairment of the lower lip and painless traumatic ulceration of the buccal mucosa along with "numb chin syndrome" has been reported.

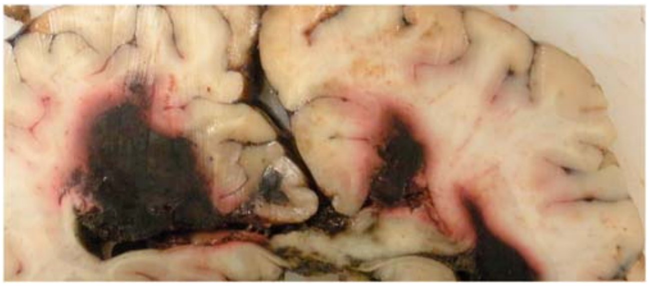

FIGURE 25-1 ■ Young male with relapse of acute B lymphoblastic leukemia complicated by multicentric intracerebral leukemic infiltrates with secondary intratumoral hemorrhage.

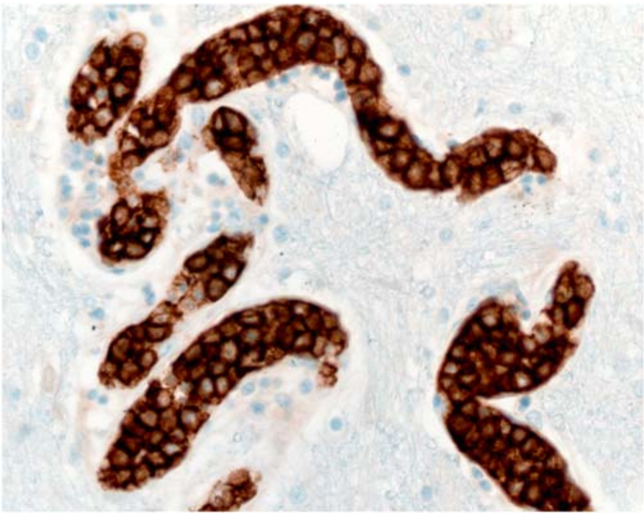

FIGURE 25-2 ■ Magnified image from Fig. 25-1 showing B-cell leukemic cells. Hematoxylin and eosin. Original magnification ×200.

Hypothalamic and pituitary dysfunction is well recognized and may be associated with hydrocephalus.

Clinically significant spinal cord involvement is unusual in leukemia; it is encountered most commonly with acute myeloid leukemia. Spinal cord syndromes arise from compression by extradural deposits; direct infiltration of the spinal cord and nerve roots; vascular occlusion by thrombus, leukemic cells, or some combination of these; or hemorrhage. Exceptionally, an acute paraneoplastic necrotizing myelopathy occurs, often with retinal changes.

Peripheral neuropathy caused directly by leukemia is rare.

CHLOROMAS (GRANULOCYTIC SARCOMA OR EXTRAMEDULLARY MYELOBLASTOMA)

Chloromas are solid tumors of nonlymphatic leukemia that are more common in children than adults. Granulocytic sarcoma develops in approximately 2.5 percent of cases of acute myeloid leukemia, and it may occur in myelofibrosis or myelodysplastic syndromes as part of transformation to acute leukemia. The majority of chloromas have a distinctive green color that fades on exposure to light. Most occur subperiosteally, usually in the cranial and facial bones, especially the paranasal sinuses, mastoid air cells, or orbits; they are usually attached to the dura mater and rarely invade cerebral tissue. Chloromas are radiosensitive.

INTRACRANIAL HEMORRHAGE AND THROMBOSIS

The overall incidence of intracranial hemorrhage (ICH) is around 3 percent among adult patients with hematologic malignancies. The incidence is greatest in patients with acute myeloid leukemia. Patients with intracranial lymphoma are more prone to ICH than those with acute leukemia. Chemotherapy-related endothelial injury and reduction of coagulation factors may each play a role in the pathogenesis.

Thrombocytopenia is a frequent feature of ICH and may in some cases be the result of disseminated intravascular coagulation (DIC) or leukemic infiltration of the bone marrow. Platelet production may also be impaired as a result of the myelotoxic effects of chemotherapy. Bleeding in the CNS is usually multifocal and may be confluent. DIC is a prominent feature of promyelocytic leukemia but, in other forms of leukemia, DIC is particularly marked in those with high peripheral white cell counts. It appears soon after the beginning of chemotherapy, presumably because tissue thromboplastins are released from destroyed leukocytes.

Both acute and chronic subdural hematoma may occur. Cisternal, cervical, or lumbar puncture in a thrombocytopenic patient with acute leukemia may cause a spinal subdural hematoma with resulting compression of the spinal cord or cauda equina. Cranial irradiation causes intracranial vessel narrowing and thrombotic occlusion in later life. Weakening of the vessel wall can also result in arterial dilatation and tortuosity. The sequelae of these changes are vascular malformation, aneurysmal dilatation, and arterial thrombosis.

CELLULAR HYPERVISCOSITY

Marked elevation of the white cell count may produce a significant increase in whole-blood viscosity. The signs and symptoms include headache, somnolence, and impairment of consciousness. All types of leukemia may produce this syndrome, but neurologic symptoms may occur more readily in myelogenous leukemias at lower leukocyte counts, reflecting the larger cell size.

Treatment with leukapheresis may abolish the symptoms. Blood transfusions may be hazardous because they may further elevate viscosity.

INFECTIONS

In all leukemias, but particularly in the lymphoblastic leukemia of childhood, viruses (especially mumps, measles, and varicella) are the most common infective organisms of the CNS. Bacterial and fungal infections, especially aspergillosis, also occur. The increased incidence of involvement of the CNS with rare organisms or organisms that are normally nonpathogenic is contributed to by the widespread use of corticosteroids, chemotherapy, and broad-spectrum antibiotics.

LEUKOENCEPHALOPATHY AND OTHER ENCEPHALOPATHIES

A variety of encephalopathic complications of chemotherapy, radiotherapy, and opportunistic infection are discussed in detail in Chapters 28 and 44.

Myelomatosis

Myelomatosis is the best-recognized expression of the plasma cell dyscrasias, which include Waldenström macroglobulinemia, monoclonal gammopathy of unknown significance (MGUS), paraproteinemias, plasmacytoma, plasma cell leukemia, primary amyloidosis, and the heavy-chain diseases. The major neurologic complications are: (1) compression of the spinal cord, cauda equina, or solitary nerve roots; (2) cranial nerve involvement; (3) intracranial myeloma; and (4) peripheral neuropathy. Pure meningeal myeloma is rare and presents with confusion, altered consciousness, and cranial nerve palsies. In 20 percent of cases, it is associated with plasma cell leukemia. Multiple myeloma with hyperviscosity may result in cerebral infarction.

SPINAL MYELOMA

The vertebrae are commonly infiltrated by myeloma cells, which may extend into the extradural space. Vertebral body collapse may produce neurologic deficits. Acute paraplegia sometimes occurs due to spontaneous epidural hematoma.

Extradural myeloma tumor may occur without local bone involvement, and intradural deposits may arise by spread along nerve roots via intervertebral foramina, causing radicular symptoms and signs. Spinal cord compression is sometimes caused by amyloid deposits. Infiltration of the spinal cord by myeloma cells and paraneoplastic myelopathy is rare. The lower thoracic area of the spinal cord is the most commonly affected. Patients with IgA myeloma seem to be at greater risk of spinal cord compression.

Neurologic symptoms usually develop comparatively slowly but may do so over 1 or 2 weeks. Back pain for several weeks or months commonly precedes evidence of spinal cord compression.

CRANIAL MYELOMA

Cranial myeloma is rare. The predominant sites of occurrence are the region of the sella and cavernous sinus, the body of the sphenoid, and the apex of the petrous bones. Orbital myeloma is well recognized and may present as an orbital mass with proptosis and ophthalmoplegia. Infiltration of the optic nerve may occur with features of optic neuritis. Ophthalmoplegia results from amyloid infiltration of the extraocular muscles. Primary plasmacytomas may originate in the cranial vault or the dura. Direct infiltration of the brain by myeloma cells is exceptionally rare, as is diffuse meningeal involvement.

Symptoms and signs of elevated intracranial pressure are often the earliest indications of intracranial myeloma. Other manifestations depend on the site of the lesion. Concomitant renal failure, anemia, hypercalcemia, and hyperviscosity contribute to symptoms.

PERIPHERAL NEUROPATHY

Five types of neuropathy have been described in association with myelomatosis:

1. Paraneoplastic neuropathy producing demyelination and axis cylinder degeneration
2. Ischemic neuropathy due to amyloid deposition in the vasa nervorum
3. Amyloid infiltration of the peripheral nerves
4. Infiltration of the peripheral nerves by myeloma tissue
5. Drug-induced neuropathy

Neuropathy occurring in myelomatosis is heterogeneous, arising from perineural or perivascular immunoglobulin deposition, with or without amyloid infiltration. It is particularly associated with IgG and IgM myeloma. The neuropathy is a typically mild, progressive, length-dependent, symmetric, sensory, or sensory-predominant mixed neuropathy. Amyloid deposition leads to a painful small-fiber neuropathy. Direct infiltration by myeloma or amyloid tissue may produce an asymmetric or mononeuritic picture.

Although it is a complication of the established disease in diffuse myelomatosis, a paraneoplastic neuropathy is usually the presenting feature of a solitary, commonly sclerotic, plasmacytoma. This combination has a distinct male predominance. The neuropathy is usually sensory-motor, with the motor component predominating. Localized radiotherapy to the bone lesion effectively arrests and usually alleviates the neuropathy with good long-term survival.

The POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) is a type of plasma cell dyscrasia associated with osteosclerotic myeloma. The major criteria for the diagnosis are the presence of polyneuropathy, with a clonal plasma cell disorder, sclerotic bone lesions, elevated vascular endothelial growth factor (VEGF), and the presence of Castleman disease (lymphoid hyperplasia with marked follicular capillary proliferation and endothelial hyperplasia, which may be restricted to a single lymph node or may be a more generalized lymphadenopathy). POEMS syndrome should be distinguished from the Castleman disease variant of POEMS syndrome, which has no clonal plasma cell disorder and typically little or no peripheral neuropathy. POEMS syndrome can be distinguished from standard multiple myeloma by a number of features; the dominant symptoms are typically neuropathy, endocrine dysfunction, and volume overload. Bone pain, extremes of bone marrow infiltration by plasma cells, or renal failure are not major features. VEGF levels are high (and correlate with disease activity), sclerotic bone lesions are present in the majority of cases, overall survival is better, and lambda clones predominate.

The bone marrow contains less than 5 percent plasma cells in POEMS syndrome (in multiple myeloma, the bone marrow contains more than 10% plasma cells) but demonstrates megakaryocyte hyperplasia and clustering reminiscent of a myeloproliferative disorder (significantly, the *JAK2* V617F mutation is absent). Patients with osteosclerotic myeloma usually have multiorgan involvement including skin change, lymphadenopathy, papilledema, peripheral edema, hepatomegaly, splenomegaly, and ascites. New criteria have been developed for POEMS syndrome and any patient with a diagnosis of chronic inflammatory demyelinating polyneuropathy not responding to standard therapy should undergo investigations to rule in or exclude the diagnosis of POEMS syndrome.[3]

The neuropathy is of a symmetric sensory-motor demyelinating type, with clinical similarities to chronic inflammatory demyelinating polyneuropathy, including an elevated CSF protein concentration. Possibly as a result of thrombocytosis, there is a 13 percent risk of stroke over 5 years.

A particularly localized form of neuropathy due to infiltration of the carpal tunnel by amyloid deposits is well recognized. Concurrent neuropathy and myositis due to sarcolemmal deposits of IgD in IgD myeloma has been described.

Neuropathy may also be a consequence of drug treatments for myeloma. Thalidomide induces a length-dependent sensory-motor neuropathy with autonomic involvement in 70 percent of patients treated for 12 months. Bortezomib and vincristine may also result in neuropathy, although there appears to be an interaction between myeloma-related factors and the patient's genetic background in the development of treatment-induced peripheral neuropathy.

Neurologic Effects of Metabolic Complications

Neurologic complications may result from hypercalcemia, uremia, and hyperviscosity. Symptomatic hyperviscosity is much more common in Waldenström macroglobulinemia (10 to 30%) than it is in myeloma (2 to 6%). Symptoms of hyperviscosity usually appear when the normal serum viscosity of 1.4 to 1.8 centipoise (cP) reaches 4 to 5 cP, corresponding to a serum IgM level of at least 3 g/dL, an IgG level of 4 g/dL, and an IgA level of 6 g/dL.

Hypercalcemia and uremia cause increasing headaches, confusion, disorientation, somnolence, stupor, coma, uremic convulsions, and myoclonic twitching.

Neurologic Complications of Immunodeficiency

Immunodeficiency is a common feature of myelomatosis. In the CNS, this is reflected by the development of meningitis (bacterial, viral, fungal) and cerebral abscess. Pneumococcal infection is particularly implicated, as is herpes zoster virus and, more rarely, cryptococcosis and toxoplasmosis. Profound septicemia may be complicated by cerebral DIC. Progressive multifocal leukoencephalopathy may also occur.

Macroglobulinemia (Waldenström Disease)

This is a lymphoplasmacytic lymphoma with IgM monoclonal protein. Almost all patients have a preceding phase of IgM MGUS. Clinical features include anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy, and rarely hyperviscosity. The L265P mutation in the *MYD88* gene is found in more than 90 percent of cases, approximately 50 percent of patients with IgM MGUS, and the majority of patients with anti-MAG paraprotein-associated peripheral neuropathy, sometimes in the absence of an identifiable IgM MGUS.

Neurologic symptoms occur in 25 percent of patients with macroglobulinemia. An antibody-related neuropathy is found in 5 to 10 percent of cases and is associated with IgM kappa antimyelin-associated glycoprotein antibodies. Other mechanisms such as lymphocytic infiltration of the peripheral nerves, amyloidosis, and a bleeding tendency may also result in neuropathy.

Bing Neel syndrome is a rare disease manifestation of Waldenström macroglobulinemia, usually presenting as a feature of relapsing disease, although it may occur at first diagnosis. Malignant lymphoplasmacytic cells invade the CNS. Cells may be found in the CSF, the meninges, and/or the cerebral parenchyma. Symptoms are progressive and reflect involvement of the central and, rarely, the peripheral nervous system. Headache, nausea and vomiting, visual disturbances, hearing loss, and cranial neuropathies, mostly of the facial or oculomotor nerves, usually accompany meningeal involvement. Seizures, cognitive decline, aphasia, psychiatric symptoms, cerebellar dysfunction, impairment of consciousness including coma, and sensory and motor symptoms and signs result from involvement of the brain and spinal cord.

Other neurologic complications relate to hyperviscosity and bleeding tendency. Exceptionally, Waldenström disease is complicated by primary intracerebral lymphoma, progressive multifocal leukoencephalopathy, or a humorally mediated immune myopathy from IgM-κ antibodies directed against muscle surface protein. A wide range of therapies are available, many of which have neurotoxicity.

Light/Heavy-Chain Deposition Disease

A variety of lymphoplasmacytic processes may produce abnormal light or heavy chains such as chronic lymphocytic leukemia or lymphoma and nodal marginal cell lymphoma. These may be the result of the emergence of a mutated clone of plasma cells that occurs after the use of certain chemotherapeutic agents such as melphalan. Light/heavy-chain deposition disease may occur in the absence of detectable underlying systemic neoplastic lymphoproliferative processes, even after prolonged follow-up for more than 10 years. Light-chain deposition disease may be associated with a local clone of plasma cells (extramedullary plasmacytomas), most commonly in the sixth decade.

Peripheral neuropathy is found in approximately 20 percent of cases. Light-chain deposits may be seen in the endoneurium. In cases of light-chain deposition disease, peripheral nerve involvement has been reported occasionally. Serum-free light-chain testing is more sensitive than urine electrophoresis for diagnosis.

Paraproteinemias

Monoclonal gammopathy of unknown significance (MGUS) is characterized by low-titer (<3 g/dL) bands of IgM, IgG, or IgA. They are found in 1 percent of healthy individuals over the age of 25 years, increasing to 3 percent in those over 70 years. The majority are IgG; less than 15 percent are IgM. The somatic point mutation of the *MYD88* gene has been identified in more than 90 percent of patients with Waldenström macroglobulinemia, in approximately 50 percent of patients with IgM MGUS, and the majority with anti-MAG neuropathy, not all of whom have an identifiable IgM MGUS. The prevalence of MGUS in those with idiopathic neuropathy is 10 percent, of which IgM accounts for 50 percent of cases, especially those with demyelinating neuropathies. Immunoelectrophoresis or immunofixation may be required to detect smaller bands. Urine light chains are rare. In MGUS, the marrow contains less than 5 percent plasma cells; blood counts are normal, and lymphadenopathy, organomegaly, and skeletal lesions do not occur. Investigation may identify primary systemic amyloidosis, myeloma, plasmacytoma, macroglobulinemia, cryoglobulinemia, lymphoma, or lymphoproliferative disorder. Approximately one-third of patients with MGUS will develop myeloma, macroglobulinemia, amyloidosis, or a lymphoproliferative disorder over 20 years; this is sometimes heralded by an unusually rapid, progressive course of the neuropathy. The risk of progression of MGUS to multiple myeloma or related disorders is influenced by the underlying cytogenetic type; patients with t(4;14) translocation, del(17p), and gain(1q) are at a higher risk of progression to multiple myeloma.

Approximately 5 percent of patients with MGUS will develop a polyneuropathy, associated in the majority with an IgM band. The median age of onset is in the sixth decade with a slowly progressive, distal, symmetric sensory–motor polyneuropathy or, less commonly, a predominantly sensory neuropathy. A presentation resembling chronic inflammatory demyelinating polyneuropathy is well recognized, although this condition differs from the typical form due to more dominant sensory symptoms, an older age at onset, and a slower, more progressive course. Neurophysiologic studies commonly demonstrate a mixed axonal and demyelinating picture. Predominant axonal degeneration is uncommon; pure demyelination is particularly associated with IgM MGUS. CSF protein levels may be markedly elevated.

Antibody to MAG expressed on Schwann cells may be seen with lymphoid malignancy such as myeloma, plasmacytoma, or Waldenström macroglobulinemia, and in as many as half of the cases of IgM MGUS. The neuropathy has a particular phenotype of a distal acquired demyelinating symmetric sensory and motor neuropathy. About 17 percent of patients with anti-MAG neuropathy present with an atypical clinical phenotype including acute or chronic sensorimotor polyradiculoneuropathies and asymmetric or multifocal neuropathy. It is slowly progressive with prominent sensory ataxia and tremor. Histologically there is widening of the myelin lamellae.

The clinical pattern of antisulfatide antibody neuropathy is a sensory-predominant, distal, symmetric polyneuropathy, which may be axonal or demyelinating in type. There is significant coexpression with anti-MAG antibodies. Isolated antisulfatide antibody-associated neuropathy accounts for about 5 percent of the cases of IgM gammopathy. The clinical pattern is similar to that of the neuropathy associated with anti-MAG antibodies but pain and small-fiber symptoms are more common, and they are more likely to be refractory to treatment.

Other binding specificities are described, including GM1 ganglioside and disialosyl gangliosides. If the anti-MAG assay is negative in the presence of an IgM-associated peripheral neuropathy, testing for IgM antibodies against GM1, GD1a, GD1b, GT1b, GM2, and GM3 and the paragloboside, sulfate-3-glucuronyl paragloboside (SGPG), should be undertaken. If these antibodies are present, the probability of an association is increased but not proven. Up to 40 percent of IgM-related demyelinating neuropathies have no identifiable antibody.

IgG and IgA MGUS are less likely than IgM MGUS to be associated with identifiable antineuronal antibodies and are comparatively less common than IgM neuropathies, less likely to be demyelinating or sensory, and more likely to respond to plasmapheresis.

Chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins, and disialosyl antibodies (CANOMAD) is an IgM MGUS with a characteristic phenotype. Pathologically, antiganglioside antibodies, anti-GD1b and anti-GQ1b, produce both demyelinating and axonal features. Weakness affects oculomotor and bulbar muscles with similarities to Miller Fisher syndrome and may either be fixed or follow a relapsing-remitting course.

Lymphoma

The nervous system is involved through direct spread from primary nodal and extranodal sites. Occasionally, primary Hodgkin disease and primary non-Hodgkin lymphoma (including microglioma, reticulum cell sarcoma, and histiocytic lymphoma) of the CNS are seen. Neurologic complications result from direct invasion and compression of the nervous system or from secondary paraneoplastic syndromes. CNS involvement occurs most commonly with lymphoblastic lymphoma, large B-cell lymphoma, diffuse undifferentiated lymphoma, and diffuse histiocytic lymphoma.

SPINAL CORD AND MENINGEAL INVOLVEMENT

Spinal cord and meningeal involvement is relatively common. Extradural deposits arise as the result of direct spread from the retroperitoneal or postmediastinal spaces via the intervertebral foramina from tumor growth along nerve roots, or by direct invasion from an affected vertebral body. Intramedullary metastases of lymphoblastic lymphoma are a rare but recognized complication. The segmental arterial supply may also become compressed, resulting in ischemic myelopathy. Rarely, an acute necrotizing myelopathy appears as a remote paraneoplastic effect of a lymphoma. Subacute paraneoplastic myelopathy may occur in Hodgkin disease.

Spinal cord segments C5 to T8 are most commonly involved, although compression may occur at any level, including the cauda equina. Nerve roots may be invaded and enlarged by the lymphoma, causing pain and sensorimotor segmental syndromes.

INTRACRANIAL INVOLVEMENT

Intracranial involvement usually arises from infiltration via the skull base by direct extension from involved cervical lymph nodes, or by lymphatic spread. On rare occasions, lymphoma of the skull bones spreads to form an intracranial mass. Tumor is usually found extradurally but may present as a subdural mass that sometimes invades the underlying brain, or it may be purely intracerebral. Almost all cases of lymphomatous meningitis are found in patients with diffuse non-Hodgkin lymphoma.

Meningeal lymphoma may have a protracted course with spontaneous remission. Intracranial deposits seem to be associated more often with histiocytic lymphoma, and orbital deposits more commonly with lymphocytic lymphoma. Intracranial deposits are rarely seen in lymphocytic lymphoma unless leukemia has supervened.

PARANEOPLASTIC SYNDROMES AND OTHER NEUROLOGIC COMPLICATIONS

A range of paraneoplastic syndromes and treatment-associated complications associated with the lymphomas are discussed in Chapters 27 and 28.

Burkitt Lymphoma

Burkitt lymphoma is an aggressive peripheral B-cell lymphoma. It is endemic in equatorial Africa where it is frequently found in children with reduced immunity to Epstein–Barr virus (EBV), often affecting the mandible. It is found internationally in a sporadic form in adolescents and young adults, but is also common in individuals infected with human immunodeficiency virus (HIV); 90 percent of the endemic form, 20 percent of sporadic cases, and 40 percent of HIV-related cases are associated with EBV infection, which causes an upregulation of *c-myc*, a gene controlling transcription regulation.

Burkitt lymphoma is frequently complicated by nervous system involvement, most commonly paraplegia, cranial neuropathies, and CSF pleocytosis. Tumor spreads through the bones of the face, skull, and orbit and along cranial nerves. Spinal cord compression from direct extension from the vertebral bodies or via the intervertebral foramina is well recognized, and ischemic myelopathy may result from compression of radicular arteries. Patients with facial tumors are likely to develop orbital involvement and ophthalmoplegia. Infiltration of the skull base may produce other cranial nerve palsies and an inflammatory CSF.

Primary CNS Lymphoma

Primary CNS lymphoma (PCNSL) is rare, accounting for about 2.5 percent of primary brain tumors. Recently reported incidence rates in the United States population increased from 0.02/100,000 persons in the first two decades of life, to 0.3/100,000 in patients aged 35 to 44 years, and up to 2.13/100,000 in patients 75 to 84 years old. The incidence amongst HIV-positive individuals has dropped markedly, but PCNSL rates have increased among immunocompetent elderly adults.

Bruton tyrosine kinase, which links the B-cell antigen receptor and Toll-like receptors with NF-κB, may play a critical and therapeutically important role. This pathway is frequently affected by mutations in *MYD88* and *CD79B*. Other mutations suggest that immune invasion might also play a role in PCNSL.

Although all cytologic types are observed, 90 percent belong to the high-grade category of non-Hodgkin lymphoma, the majority being clonal and of B-cell origin, as evidenced by their monoclonal expression of either κ or λ light-chain immunoglobulin. Less common histologic types include low-grade lymphomas, Burkitt lymphomas, and T-cell lymphomas.

Non-Hodgkin PCNSL has an extremely poor prognosis. Tumor masses are usually multicentric and ill-defined. Immunocompromised individuals are at greatest risk. The incidence of these tumors is increasing, and their association with HIV only partly accounts for this rise. Primary CNS lymphoma in immunodeficient patients is often associated with EBV, which is detected frequently in the CSF.

Imaging displays discrete, often large, enhancing tumors with bilateral hemispheric involvement spreading through the corpus callosum. Despite the fact that these tumors are highly radiosensitive, the prognosis for PCNSL is worse than for other extranodal lymphomas, and late morbidity and mortality may occur from radiation necrosis. Treatment with chemotherapy and radiation usually leads to remission but with a significant recurrence rate.

Primary lymphoma of the spinal cord is exceptionally rare, as is primary lymphoma of the nerve roots, including the cauda equina.

Peripheral neuropathy of the paraneoplastic type may occur in association with PCNSL.

Intravascular Lymphoma

Intravascular lymphoma is a rarely diagnosed subtype of generalized lymphoma. It is characterized by proliferation of blastic, neoplastic B cells within the lumina of small- or intermediate-sized blood vessels and capillaries, producing vascular occlusion of arterioles, capillaries, and venules (Figs. 25-3 and 25-4). There is a high prevalence of *MYD88* and *CD79B* mutations. More than 25 to 50 percent of cases present with neurologic symptoms, and two-thirds develop neurologic symptoms during the course of the disease. The presentation may be diffuse or focal, and suggestive of vascular disease. Dementia, stroke-like episodes, myelopathy, cranial neuropathy, peripheral neuropathy, and brainstem syndromes predominate. Establishing the diagnosis is often difficult because of marked variability in clinical presentation and nonspecific laboratory and radiologic findings, especially when CNS symptoms are the only manifestation. Imaging demonstrates multifocal lesions in the brain suggestive of microvascular or demyelinating disease. Angiography may

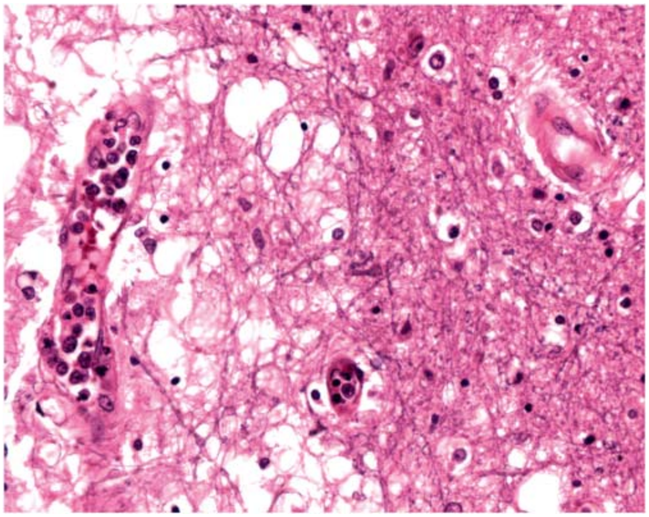

FIGURE 25-3 ■ Intravascular lymphoma. Section showing focus of cerebral ischemia with blood vessels plugged by large atypical lymphocytes (on left). Vessels in adjacent brain (right) not affected. (Hematoxylin and eosin. Original magnification × 400.)

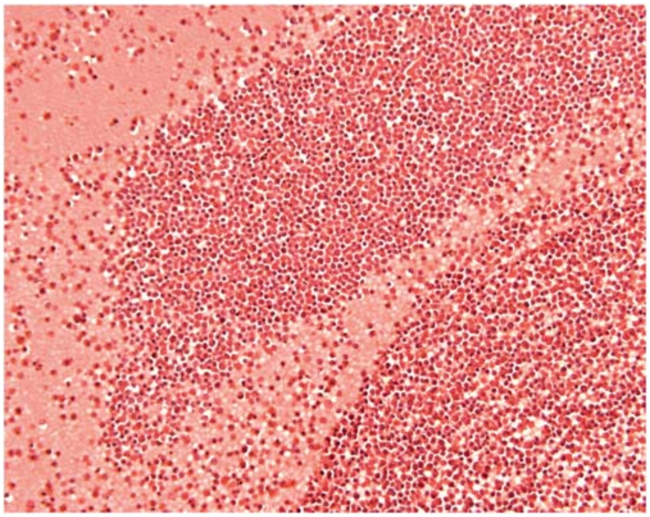

FIGURE 25-4 ■ Immunostained brain section showing distension and plugging of intracerebral vessels by CD20-stained malignant B-lymphocytes confirming intravascular lymphoma. (Original magnification ×400.)

show a beaded appearance reminiscent of vasculitis. The CSF findings are nonspecific, and cerebral biopsy should be undertaken in suspected cases.

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis is a rare aggressive angiocentric and angiodestructive EBV-positive B-cell lymphoproliferative disease involving predominantly the lung. It is thought to be caused by dysregulated immune surveillance of EBV. It is uncertain whether it represents a unique disease or is part of the spectrum of EBV B-cell lymphoproliferative diseases. The nervous system is involved in one-third of patients, with occasional cases isolated to the CNS. It may occur in patients with Sjögren syndrome, chronic viral hepatitis, rheumatoid arthritis, renal transplantation, and HIV infection. The usual presenting symptoms are fever, weight loss, malaise, cough, dyspnea, and neurologic symptoms, which can include encephalopathy, seizures, hemiparesis, cranial neuropathy, optic neuropathy, peripheral neuropathy, and mononeuritis multiplex. Pathologically, there is a nodular polymorphic mononuclear cell infiltrate with prominent vascular infiltration and often necrosis. Varying numbers of large, often atypical, CD20-positive B-lymphocytes are present within a background containing numerous polyclonal reactive CD3-positive small T-lymphocytes and scattered admixed plasma cells in the meninges and cerebral blood vessel walls within the brain parenchyma and along nerve roots and peripheral nerves. The appearance may mimic vasculitis and can result in vascular occlusion. Morphologically, there is an overlap in higher-grade forms (grades 2 and 3) with variants of large B-cell lymphoma, and multiple lesions in a single patient may show wide variation in histologic grade. Treatment depends on grade, with grade 3 being managed as diffuse large B-cell lymphoma.

Polycythemia

A group of conditions previously thought to be distinct entities has been shown to have a common genetic etiology in exon 14 V617F mutations of the *JAK2* (Janus kinase 2) gene, including essential polycythemia, essential thrombocythemia, and myelofibrosis—the classic *bcr/abl*-negative myeloproliferative disorders. Each disease represents a stem cell–derived clonal myeloproliferation. The presence of this *JAK2* mutation may be used as a diagnostic test. Approximately 5 percent of patients who test negative for the *JAK2* exon 14 V617F mutation have one of a number of mutations known collectively as the *JAK2* exon 12 mutations.

There are many causes of polycythemia, including erythropoietin-producing neoplasms and nonmalignant renal cysts and inappropriately elevated erythropoiesis induced by hypoxemia such as from right-to-left cardiac or pulmonary shunts.

An increased incidence of thrombotic and hemorrhagic complications is a well-recognized phenomenon in polycythemia, in part arising from accelerated atherosclerosis. There is growing evidence that the increased risk of thrombosis is not caused directly by erythrocytosis alone but by interactions amongst white cells, red cells, platelets, and endothelium, with increased blood viscosity, reduced perfusion, vascular engorgement, atheromatous degeneration of vessel walls, and possibly chronic DIC. Patients with polycythemia whose hematocrit is below 45 percent have a significantly lower rate of cardiovascular death and major thrombosis than those with a hematocrit of 45 to 50 percent. Approximately 15 percent of patients with polycythemia die of cerebral thrombosis, 87 percent of them after repeated episodes. Thromboembolism often continues to be a major clinical problem even after hematologic control has been achieved. Hemorrhage may be related to imperfect clot retraction, abnormal thromboplastin generation, and abnormalities of platelet count and function. CNS hemorrhage may be cerebral, epidural, subdural, or subarachnoid.

The clinical course of polycythemia vera is often complicated by the transition to myeloid metaplasia with myelofibrosis or acute myeloid leukemia.

Nonspecific symptoms of fullness in the head, vertigo, tinnitus, and lack of concentration are common. More specific signs such as hemiparesis, hemianesthesia, hemianopia, and aphasia depend on the site of infarction or hemorrhage. Brainstem vascular syndromes occur, as do bulbar and pseudobulbar palsy, convulsions, and coma. Amaurosis fugax, blindness, scotomas, and cerebral or brainstem TIA are features as well. More rarely, signs and symptoms of a progressive cerebral lesion arise because of a subdural hematoma, an expanding intracerebral blood clot, or cerebral infarction accompanied by edema. Distention and congestion of the retinal veins, central retinal venous or arterial occlusion, and papilledema may be present. Idiopathic intracranial hypertension has been reported. Aseptic cavernous sinus thrombosis associated with internal carotid artery occlusion may occur; treatment with repeated phlebotomies and heparin may result in resolution of proptosis, pain, periorbital edema, lacrimation, venous congestion, ptosis, and ophthalmoplegia, and may restore sight. The one-and-a-half syndrome may occur and has been ascribed to brainstem ischemia.

Transient spinal cord ischemia may be the presenting feature of polycythemia vera, but spinal cord infarction is an exceptionally rare complication. Spinal cord compression due to spontaneous subdural hematoma and extramedullary hematopoiesis in the proliferative phase of polycythemia is uncommon.

Chorea, dystonia, and hyperkinetic movement disorders are also uncommon complications of polycythemia. Chorea may be of sudden onset and tends to occur in women older than 50 years. It may resolve before any significant reduction of the red cell count, but more often it resolves with correction of the polycythemia. The chorea is generalized, with predominant involvement of the face, mouth, tongue, and arms. It is not apparently related to the rare finding of a small infarct in the caudate nucleus.

A prospective clinical and electrophysiologic study of 28 patients with polycythemia identified 46 percent with clinical features of neuropathy and 71 percent with neurophysiologic evidence of sensory axonal polyneuropathy, probably arising from endoneurial ischemia. Oculomotor nerve paresis as a presenting sign of acute myeloblastic leukemia complicating polycythemia has been reported.

Mutations in the *SLC30A10* gene, which is highly expressed in the liver and brain and encodes a protein belonging to a large family of membrane transporters, may result in polycythemia with parkinsonism and dystonia.

Cerebellar Hemangioblastoma

Cerebellar hemangioblastoma may be associated with polycythemia, and 34 percent of these patients have von Hippel–Lindau disease, which is caused by mutations in the *VHL* gene. Germline mutations of the *VHL* gene can arise de novo in approximately 5 percent of cases. The VHL protein is involved in the inhibition of hypoxia inducible factor 1 α, which accumulates, causing the production of vascular endothelial growth factor, platelet-derived growth factor B, erythropoietin, and transforming growth factor α. von Hippel–Lindau disease is subdivided according to clinical manifestations, which largely correlate with the types of mutations present. Type 1 mostly have hemangioblastoma and renal carcinoma, but pheochromocytomas are rare. Patients with type 2A are at risk of both hemangioblastoma and pheochromocytoma, but not renal carcinoma. Those with type 2B are at risk of all three tumors, with a higher risk of clear-cell renal carcinoma; persons with type 2C are only at risk of pheochromocytoma. Type 3 disease has a risk of Chuvash polycythemia.

The symptoms of cerebellar hemangioblastoma are those of increased intracranial pressure and "dizziness," with either truncal and gait ataxia or hemiataxia with accompanying nystagmus. Neck stiffness and rarely cerebellar "fits" may occur. On examination, the symmetric or lateralized cerebellar ataxia is associated with papilledema, hemiparesis, bilateral pyramidal signs, or any combination of deficits from cranial nerve V, VI, VII, or VIII involvement. Recurrence many years after surgical treatment is typical of hemangioblastoma.

Pseudopolycythemia

Pseudopolycythemia is a condition in which an increased hematocrit is associated with normal red cell mass; plasma volume may be reduced in the absence of apparent fluid loss, related to aberrations in catecholamine metabolism. It is associated with hypertension, obesity, and stress, especially in middle-aged men who are smokers. In this condition, as in polycythemia, there is an increased risk of thromboembolism arising from an increase in whole-blood viscosity and reduced cerebral blood flow. In patients with a packed cell volume exceeding 54 percent, regular venipuncture with withdrawal of 100 to 250 ml blood is recommended to reduce the packed cell volume to around 46 percent.

Essential Thrombocythemia

Essential thrombocythemia is a clonal stem cell disorder with overproduction of megakaryocytes. Mutations in the *JAK2*, *CALR*, and *MPL* genes account respectively for 55, 25, and 3 percent of cases. Approximately 17 percent are triple-negative. The presence of *JAK2*V617F has been associated with an increased risk of arterial thrombosis and a lower risk of subsequent myelofibrosis.

Essential thrombocythemia is characterized more frequently by thrombotic than hemorrhagic complications; the presence of extreme thrombocytosis (platelets $>1{,}000 \times 10^9/\text{L}$) may be associated with acquired von Willebrand syndrome and a risk of bleeding.

The condition is diagnosed on the basis of a persistently elevated platelet count without evidence of trauma, inflammation, hemorrhage, hyposplenism, or any other condition known to be associated with thrombocytosis. Amaurosis fugax, transient hemiparesis or hemianesthesia, recurrent vertigo, and confusion are the characteristic symptoms. Most patients have circulating platelet aggregates or spontaneous platelet aggregation, and reduced platelet survival. Considerable clinical improvement can be achieved with antiplatelet drugs and, where appropriate, by reduction of platelet count. Evolution to myelofibrosis occurs in 3 to 10 percent of patients in the first decade after diagnosis, and in 6 to 30 percent in the second decade. Progression to acute myeloid leukemia occurs in 1 to 2.5 percent in the first decade after diagnosis, 5 to 8 percent in the second decade, and continues to increase subsequently, though this may be a consequence of treatment rather than due to the underlying disorder.

Myelofibrosis

Myelofibrosis is an uncommon myeloproliferative disorder arising predominantly in patients older than 50 years and characterized by replacement of the bone marrow by fibrous tissue. Activation of the JAK/STAT signaling pathway is a hallmark feature of myelofibrosis, and is driven by mutations in *JAK2*, *CALR*, and *MPL*. It is associated with extramedullary hematopoiesis and marked hepatosplenomegaly. Patients are anemic, may be slightly jaundiced, and have a leukoerythroblastic blood picture. Neurologic complications are rare. A number of reports describe meningeal hematopoietic masses. Spinal cord compression from extramedullary hematopoiesis is recognized but uncommon.

Eosinophilic Syndromes

Eosinophilia is defined as an increase in peripheral blood eosinophil count to greater than 450 cells/μL, with accompanying eosinophilic infiltration of muscle, nerve, or CSF. Eosinophilia may be observed in a wide range of conditions (Table 25-1).

Eosinophilic infiltration into skeletal muscle is rare. It has been described in parasitic infection as focal eosinophilic myositis, in systemic hypereosinophilic conditions such as the eosinophilia-myalgia syndrome, and in idiopathic hypereosinophilic syndrome. Diffuse fasciitis or Shulman syndrome can be limited to the fascia or associated with perimyositis. Eosinophilic myositis corresponds to focal muscle involvement, and it is associated with skin lesions in approximately 40 percent of cases, including deep subcutaneous induration, erythema, angioedema, urticaria, and papular lesions. The overall prognosis of eosinophilic myositis is good, particularly when muscle lesions are focal, and the principal histopathologic finding is perimysial infiltrates.

Compound heterozygous or homozygous *CAPN3* mutations have been found in a subgroup of children in the first decade of life with autosomal recessive inheritance, variable peripheral eosinophilia, and elevated serum creatine kinase levels, but with little or no weakness. The *CAPN3* gene encodes calpain-3, a muscle-specific intracellular nonlysosomal protease. Mutations in this gene are responsible for the commonest autosomal recessive limb-girdle muscular dystrophy, calpainopathy (LGMD2A). Very rare cases of adult-onset eosinophilic polymyositis have now been described with mutations in the calpain-3 gene. Whether this represents the well-known inflammatory feature of muscular dystrophy or is a true eosinophilic myositis is uncertain.

TABLE 25-1 ■ Nervous System Involvement With Eosinophilic Syndromes

- Trichinosis
- Eosinophilic meningitis or meningoencephalitis (angiostrongyliasis, gnathostomiasis, visceral larva migrans)
- Connective tissue diseases
    - Churg–Strauss vasculitis
    - Eosinophilic fasciitis
    - Polyarteritis nodosa
- Eosinophilia-myalgia syndrome (due to tryptophan in the United States in 1989)
- Toxic-oil syndrome (due to contaminated rapeseed oil in Spain in 1981)
- Coccidioidomycosis
- Helminth infections
- Ascariasis
- Schistosomiasis
- Trichinosis
- Visceral larva migrans
- Gnathostomiasis
- Strongyloidiasis
- Fascioliasis
- Paragonimiasis
- Neoplasia
    - Lymphoma (e.g., Hodgkin lymphoma, non-Hodgkin lymphoma)
    - Human T-cell lymphotropic virus I (HTLV-I)
    - Adult T-cell leukemia/lymphoma (ATLL)
    - Eosinophilic leukemia
    - Gastric or lung carcinoma (i.e., paraneoplastic eosinophilia)
- Allergic/atopic diseases
- Adrenal insufficiency in ill patients

When it is a manifestation of the hypereosinophilic syndrome, eosinophilic myositis may be life-threatening. Hypereosinophilic syndrome is a heterogeneous group of rare disorders defined by persistent blood eosinophilia of at least 1,500 eosinophils/μL without a cause, along with evidence of eosinophil-associated organ damage. There are a number of subtypes which may overlap with chronic eosinophilic leukemia. These subtypes are associated with dramatic differences in clinical presentation, prognosis, and responses to therapy. Abnormal or clonal T-cell populations are present in 17 percent of cases. There is pathologic evidence of multiorgan infiltration by eosinophils. Cardiac disease is common with valvular disease resulting in embolization. Systemic manifestations other than eosinophilia include anemia, hypergammaglobulinemia, vascular involvement (subungual petechiae, livedo reticularis, diffuse microangiopathy, Raynaud phenomenon), skin rash and subcutaneous edema, pulmonary infiltrates and pleuritis, cardiac involvement (congestive heart failure, arrhythmias, heart block, pericarditis, myocardial and endocardial fibrosis), and peripheral neuropathy. One-third of the patients have neurologic symptoms such as encephalopathy, multiple cerebral infarcts (possibly embolic in origin), peripheral neuropathy, and mononeuropathy multiplex. Patients may respond well to corticosteroids. Additional agents that have been used to rapidly lower counts in steroid-refractory patients include high-dose hydroxyurea, vincristine, and mepolizumab (humanized anti-interleukin-5 antibodies).

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a rare nonmalignant syndrome of pathologic immune activation. It is characterized by uncontrolled proliferation of T lymphocytes, NK cells, and macrophages, with infiltration of multiple organs including the CNS. Excessive activation of $CD8^+$ T lymphocytes results in the release of tumor necrosis factor-α, IL-1β, IL-6, IL-8, and interferon-gamma. It occurs most commonly in children aged under 1 year. Primary HLH is caused by loss of function in a variety of genes required to kill virus-infected cells. Secondary HLH is associated with malignancy, infections, and a range of immunosuppressive disorders and therapies. It may contribute to the hyperinflammation seen in H1N1 and H1N5 influenza outbreaks. It has been described within a few months to 4 years of treatment with alemtuzumab for relapsing-remitting multiple sclerosis.

It is diagnosed by either a proven genetic mutation or by fulfilling at least five of eight clinical criteria; fever, splenomegaly, cytopenias of at least two cell lines, hypertriglyceridemia and/or hypofibrinogenemia, hyperferritinemia, abnormally low NK-cell activity, high levels of soluble IL-2 receptor, and pathologic evidence of hemophagocytosis in tissues.

Seizures, irritability, disturbance of consciousness, and encephalopathy are common. Meningism is reported in approximately one-third of patients. Focal signs, such as hemiparesis, cranial neuropathies, and ataxia, are seen in 10 to 20 percent of cases.

The differential diagnosis for CNS HLH includes acute disseminated encephalomyelitis, acute necrotizing encephalopathy, CNS vasculitis, multiple sclerosis, encephalitis, CNS manifestations of rheumatologic disease (such as systemic lupus erythematosus; SLE), and other genetically mediated CNS inflammatory disorders such as interferonopathies.

CNS disease has been divided into three stages: stage I with leptomeningeal inflammation, stage II with perivascular infiltration, and stage III with massive tissue infiltration, blood vessel destruction, and tissue necrosis. Treatment is with immuno- and chemotherapy followed by hematopoietic stem cell transplantation.

Macrophage Activation Syndrome

The similarities between primary HLH and macrophage activation syndrome (MAS) are striking. Although the final pathways are shared, the initiating factors may be different. Both are characterized by widespread inflammation and end-organ damage. MAS is classically associated with rheumatologic conditions such as systemic juvenile idiopathic arthritis and adult-onset Still disease, in contrast to HLH which is characteristically associated with viral infections, malignancy, and certain chemotherapies. Mutations in genes associated with the lymphocyte cytolytic pathway are common to both syndromes, and both MAS and HLH present clinically with marked hyperferritinemia, cyclic fevers, cytopenias, hepatosplenomegaly, coagulopathy, and if not treated, end-organ failure and death.

Characteristic clinical features of MAS are high, nonremitting fever, hepatosplenomegaly, generalized lymphadenopathy, hemorrhage, and CNS dysfunction in 35 percent, including seizures, headache, or encephalopathy.

NEUROLOGIC COMPLICATIONS OF THERAPIES FOR HEMATOLOGIC MALIGNANCIES

Chimeric Antigen Receptor T-Cell Therapies

Chimeric antigen receptor (CAR) T cells (CAR-T) have emerged in recent years as powerful treatments for relapsed and refractory hematologic malignancies. CAR-T cells are engineered to express synthetic receptors that redirect polyclonal T cells to surface antigens for tumor elimination. Many CARs are designed with elements that augment T-cell persistence and activity. A variety of targets have been used including CD19 in B-cell ALL, Burkitt lymphoma and non-Hodgkin lymphoma, CD22 in B-cell malignancies, and B-cell maturation antigen in multiple myeloma.

Toxicity occurs as two related but distinct syndromes: a cytokine release syndrome and neurotoxicity, referred to as immune effector cell therapy–associated neurotoxicity syndrome (ICANS).

Cytokine release syndrome is a multisystem clinical syndrome characterized by fever, hypotension, hypoxia, and in more severe cases multisystem organ dysfunction. It is caused by the release of proinflammatory cytokines by the activated CAR-T cells. CRS is extremely common; in some trials, 100 percent of patients experienced at least some symptoms of CRS. Treatment with tocilizumab, which blocks the IL-6 signal receptor pathway, can effectively mitigate the symptoms of CRS without impairing the antitumor efficacy of the CAR-T cells. Neurotoxicity associated with CAR-T cell therapy includes encephalopathy (57%), headache (42%), tremor (38%), aphasia (35%), and focal weakness (11%). The mortality rate depends on patient selection and therapy, but a recent series suggested 5 percent. Focal neurologic deficits are associated with regional electroencephalographic abnormalities, FDG-PET hypometabolism, and elevated velocities on transcranial Doppler ultrasound. Structural imaging is frequently normal.[4]

Neurotoxicity may fluctuate with fever and recur after cytokine release symptoms have subsided. Clinical or subclinical seizures may develop, often following the development of global aphasia. Cerebral edema may follow seizures and may commence with a fulminant onset.

A consensus grading system for CRS and ICANS has been developed to enable monitoring and to identify neurotoxicity requiring treatment.[5]

Checkpoint Inhibitors

The tumor microenvironment in most lymphomas and solid cancers has multiple mechanisms for inhibiting an efficient immune response against it.

PD-1 is a negative regulator of T-cell activity and limits the activity of T cells by interaction with its two ligands, PD-L1 and PD-L23. When PD-1 is engaged by one of these ligands, it inhibits kinase signaling that leads to T-cell activation, thereby suppressing T-cell function.

CTLA-4 competitive binding can prevent the co-stimulatory signal normally provided by CD28:B7 binding. This stops potentially autoreactive T cells at the initial stage of naive T-cell activation, typically in lymph nodes.

Inhibitors of PD-1 and CTLA-4 are now being used to treat a range of solid tumors, particularly metastatic melanoma, lung cancer, and hematologic malignancies.

The immune checkpoint inhibitor pembrolizumab is a highly selective, humanized monoclonal immunoglobulin G4/κ antibody that blocks the interaction between PD-1 and its ligands. A range of neuroimmunologic complications has been described including limbic encephalitis, chronic inflammatory demyelinating polyneuropathy, myasthenia, necrotizing myelopathy, and subacute multifocal CNS demyelination.

Ipilimumab is a human $IgG_1κ$ monoclonal antibody specific for CTLA-4 expressed on activated T cells. Checkpoint inhibitors to CTLA-4 can result in a range of neurologic disorders including Guillain–Barré syndrome, myasthenia, transverse myelitis, encephalopathies, and autoimmune meningoencephalitis.

Combined use of PD-1 inhibitors and CTLA-4 inhibitors may induce anti-NMDA (*N*-methyl-D-aspartate) receptor encephalitis, which was not seen when the agents were used individually.

Myasthenia seems commonly to be triggered by checkpoint inhibitors. The literature suggests 72.7 percent are de novo presentations, 18.2 percent are exacerbations of pre-existing myasthenia gravis, and 9.1 percent are exacerbations of subclinical myasthenia. Only 60 percent were seropositive for acetylcholine receptor antibodies. A 30 percent myasthenia-specific related mortality, probably a result of multiple morbidities, emphasizes the need for vigilance.

With increasing use of checkpoint inhibitors and their predilection for triggering exacerbations of pre-existing or de novo autoimmunity, neurologic autoimmunity is likely to occur more frequently, and any relationship between the resulting disease and the malignancy and mechanism of checkpoint inhibitor is likely to become clearer.[6,7]

HEMORRHAGIC DISORDERS

Hemophilia A

The severity of bleeding in hemophilic patients correlates with the factor VIII level. Severely affected hemophiliacs with levels of less than 1 percent commonly have spontaneous bleeding into muscles and joints. With factor VIII levels of 1 to 5 percent, spontaneous bleeding is much less frequent. Patients with factor VIII levels greater than 10 percent can lead normal lives, as excessive blood loss occurs only after more severe trauma and surgery. Hypertension is an important additional factor in older patients. Lyonization (X-inactivation) may result in severe factor VIII deficiency in some females.

Intracranial bleeding is the leading cause of death. The incidence of intracranial hemorrhage ranges approximately from 2 to 14 percent. Bleeding tends to occur predominantly in young hemophiliacs, and may occur into the subdural, epidural, or subarachnoid spaces or into the cerebral or cerebellar hemispheres and brainstem. The symptoms and signs depend on the site of the hemorrhage and its extent. Prognosis in intracranial hemorrhage has been considerably improved by the early use of factor VIII concentrates, and there is now no contraindication to surgical intervention, provided that adequate control of coagulation factors is maintained. Seizures occur in 25 percent of survivors of intracranial hemorrhage.

Bleeding into the spinal canal is rare. Patients with small epidural hemorrhages and only minimal nonprogressive signs of spinal cord dysfunction may recover completely with intensive factor VIII replacement therapy alone.

Peripheral nerve lesions are the most frequent neurologic complication of hemophilia. In most instances, nerve involvement is a complication of intramuscular hemorrhage, most commonly into the iliac muscle leading to femoral neuropathy. Median, ulnar, and radial neuropathies result from hemorrhage into the arm or forearm muscles. Nerve compression by pseudotumors (subperiosteal hemorrhages producing expanding lesions) also occurs.

Severe hemophilic arthropathy of the elbow may result in ulnar nerve palsy. Intraneural hemorrhage as a cause of peripheral nerve palsy is exceptional but may, for example, affect the ulnar nerve in the cubital tunnel. On exploration of the ulnar nerve, free blood may be seen when the epineurium is divided; recovery is rapid and complete.

During the early to the mid-1980s, many patients with severe hemophilia became infected with HIV through contaminated plasma-derived clotting factors. From 1979 to 1998, 47 percent of people with hemophilia A died of HIV-related disease.

About one-third of patients with severe hemophilia A develop neutralizing alloantibodies against factor VIII replacement treatments. Emerging treatment options for these patients include factor IXa– and factor X–directed antibody that can restore blood clotting.

Early trials of gene therapy have normalized factor VIII activity. Bleeding rates and factor VIII use were very significantly reduced in all trials.

von Willebrand Disease

von Willebrand disease is a family of related disorders characterized by deficiency or malfunction of von Willebrand factor (VWF), a protein that mediates platelet adhesion to the endothelium and protects factor VIII from degradation. An earlier age of onset is associated with more severe VWF deficiency.

There is a partial deficiency of functionally normal VWF in type 1 disease caused by heterozygous missense mutations exerting a dominant-negative effect, which results in a disturbance of the entire multimer. Almost all cases of type 2 von Willebrand disease are caused by missense mutations, and inheritance is mostly autosomal dominant. This type is associated with an increased risk of abnormal bleeding after invasive procedures. Type 2N is associated with decreased affinity of VWF for factor VIII; it is suspected when the decrease in factor VIII levels is much more profound than that of VWF, and its diagnosis is confirmed by factor VIII binding assay. There is a complete deficiency in type 3 disease. Some heterozygous carriers have mild symptoms and receive a diagnosis of type 1 disease. Patients may be either homozygous for two type 2N mutations or compound heterozygous for a type 1 defect and a type 2N defect. Rarer acquired forms are associated with hematologic malignancies, such as extreme thrombocytosis (platelets $>1000 \times 10^9/L$), SLE, and other autoimmune disorders, and with the use of valproic acid, griseofulvin, and ciprofloxacin.

The bleeding complications of von Willebrand disease are relatively mild, and spontaneous hemorrhage into joints and muscles does not occur. Acute onset of neurologic dysfunction is not a feature of this disease. Nevertheless, more significant hemorrhage may result from trauma, particularly in the rarer autosomal recessive 2N and 3 types. Patients who sustain head injuries should receive immediate factor VIII replacement therapy. The goal of treatment is to increase VWF levels by administering desmopressin or by the infusion of exogenous VWF-containing concentrates.

Hemophilia B: Factor IX Deficiency

Hemophilia B (Christmas disease) is an X-linked recessive disorder; approximately one-third of patients have no family history and have novel mutations. The neurologic complications are identical to those of hemophilia A. Thus, peripheral nerve compression occurs as a consequence of spontaneous intramuscular hemorrhage, and intracranial hemorrhage, an important cause of death in both disorders, may occur spontaneously in severely affected patients or following trauma in less severely affected individuals. Clotting factor IX is the deficient factor requiring replacement. Early trials of gene therapy using factor IX Padua transgene appear very promising, having achieved the near elimination of bleeding and of factor IX replacement therapy.

Other Clotting Factor Deficiencies

Spontaneous and post-traumatic hemorrhages are features of disorders resulting from deficiencies of other clotting factors. Surgical evacuation of any intracranial hemorrhage, when indicated, must be done in the setting of adequate replacement therapy with the relevant deficient factor or with fresh frozen plasma or cryoprecipitate if the specific factor is not available. Replacement therapy should probably be given routinely following head injuries in these patients.

Acquired Hemophilia A

Acquired hemophilia is a rare condition resulting from the production of autoantibodies against factor VIII. The mean age at diagnosis is 74 and both sexes are affected. Cutaneous purpura and internal hemorrhage are common, whereas extensive bleeding into the joints is not a prominent feature. The condition is associated with systemic autoimmune disorders; malignancies such as lymphoma, acute or chronic lymphocytic leukemias, and solid tumors; and pregnancy. Drugs such as the penicillins, phenytoin, phenylbutazones, or chloramphenicol have also been implicated. It has been reported during the immune reconstitution following the use of alemtuzumab for multiple sclerosis, sometimes years after the last infusion.

No cause can be found in around half of patients. Neurologic involvement is rare, but cases of life-threatening intracranial hemorrhage and recurrent spontaneous subdural hematoma have been reported.

The diagnosis is based on unexpected prolongation of the activated partial thromboplastin time (aPTT) and the identification of a low factor VIII level associated with the presence of a time-dependent inhibitor in the plasma. Treatment of bleeding episodes requires the use of an activated prothrombin complex concentrate or recombinant activated factor VIII. Immunoglobulin administration does not improve outcome. Immunosuppression with corticosteroids, cyclophosphamide, or rituximab achieves a 73 percent complete remission, and is usually effective at reducing inhibitor production and bringing about a sustained rise in the factor VIII level.

Hemorrhagic Disease of the Newborn

Newborns are at risk for vitamin K deficiency bleeding caused by inadequate prenatal storage and deficiency of vitamin K in breast milk. Vitamin K deficiency results in a deficiency of factors II, VII, IX, X, along with protein C and protein S. Intracranial hemorrhage is the most serious complication and occurs from the second day to the end of the first week, particularly after breech deliveries. Bleeding appears to occur from capillary lesions rather than major vessels. Subdural and subarachnoid hemorrhages are the most frequent forms of intracranial bleeding, and intracerebral hemorrhage is rare. Intracranial bleeding is reported to occur earlier and with greater frequency in infants born to mothers receiving anticonvulsant therapy, but late-pregnancy exposure to anticonvulsant drugs that induce cytochrome P-450 enzymes seems not to increase the risk in comparison with noninducing anticonvulsants. A recent systematic review of the literature on antiepileptic drug use in pregnancy concluded that evidence was insufficient to support vitamin K supplementation in the last weeks of pregnancy to reduce risk of vitamin K deficiency bleeding.

Late-onset vitamin K deficiency usually occurs 2 to 12 weeks after birth but may occur up to 6 months of age. It is associated with failure to receive vitamin K prophylaxis at birth but also occurs in exclusively breast-fed babies. The majority present with acute intracerebral bleeding.

Thrombocytopenia

If platelet function is normal, satisfactory hemostasis may be achieved with a platelet count as low as $80 \times 10^9/L$. Clinically significant spontaneous hemorrhage does not usually occur if the platelet count exceeds $25 \times 10^9/L$, but below $20 \times 10^9/L$ spontaneous hemorrhage is not uncommon. Intracerebral, subarachnoid, and subdural hemorrhages are the most serious complications; the risk of spontaneous intracranial hemorrhage appears to be greatest during the first 2 weeks after onset of the disorder. An uncommon complication of recurrent bleeding is superficial siderosis.

Drug-induced immune thrombocytopenias arise when a drug acts as a hapten, binding to platelets and resulting in complement fixation and intravascular lysis. The platelet count typically falls within 7 or more days after initiation of the responsible drug. Heparin-induced thrombocytopenia is the most common disorder of this type. It is defined as a platelet count that drops below 100 to $150 \times 10^9/L$ for no apparent reason other than heparin administration. Type I heparin-induced thrombocytopenia is characterized by a moderate reduction in platelet counts, usually within the first 7 to 12 days of the initiation of heparin therapy. The platelet count rarely drops below $100 \times 10^9/L$ and normalizes in spite of continued heparin therapy. Type II heparin-induced thrombocytopenia is immunologically mediated and paradoxically is often associated with thrombosis. Most patients produce IgG antibodies against complexes of platelet factor 4 and heparin.

Delayed-onset thrombocytopenia, a mean of 14 days after initiation of therapy is increasingly being recognized and is usually associated with heparin-induced antibodies. It may begin rapidly in patients who have received heparin any time within the previous 100 days. Heparin-dependent antibodies do not invariably reappear with subsequent heparin use. Up to 60 percent or more develop serious thrombotic complications, including ischemic damage to limbs, CNS, myocardium, and lungs. A study of 120 cases of immune-mediated heparin-induced thrombocytopenia showed that 9 percent developed neurologic complications, including ischemic cerebrovascular events (6%), cerebral venous sinus thrombosis (2.5%), and a transient confusional state in one case. Primary intracerebral hemorrhage was not observed. Importantly in three cases, neurologic complications preceded the onset of thrombocytopenia.

In severe thrombocytopenia, massive intracranial hemorrhage may be instantaneous and treatment of no avail. It is often heralded by headaches of varying severity. In these circumstances, platelet transfusion should be instituted without delay, as it should after head injury in patients with significantly reduced platelet counts.

During the immune reconstitution following the use of alemtuzumab, a humanized anti-CD52 monoclonal antibody, in the treatment of relapsing-remitting multiple sclerosis, secondary autoimmune diseases can develop, including dose-related idiopathic thrombocytopenic purpura. Between 2 and 3 percent of patients are affected within 2 years of their last infusion.

Disorders of Platelet Function

Regardless of the platelet count, abnormal bleeding states may result from abnormalities of platelet function, that is, disorders of platelet adhesion, aggregation, secretion, and procoagulant activity, or a combination of abnormalities of number and function. Bleeding due to these disorders is treated primarily with platelet transfusions.

Bernard–Soulier syndrome is an inherited, usually autosomal recessive disorder of platelet adhesion caused by deficiency of the component subunits of the glycoprotein 1b-IX-V complex. As a result, platelets fail to stick and clump together at the site of the injury, resulting in bleeding after trauma or surgery.

Glanzmann thrombasthenia is caused by the absence of platelet aggregation due to deficiencies of αIIbβ3 integrin, an aggregation receptor on platelets. This absence prevents fibrinogen bridging from occurring and thus prevents clot retraction and significantly prolongs bleeding time. It has been associated with fatal cerebral hemorrhage. Platelet count, volume, and morphology are normal in classic Glanzmann thrombasthenia, though some reports have suggested a role for αIIbβ3 in megakaryocytopoiesis, and point mutations have been described that lead to platelet anisotropy and thrombocytopenia.

The gray platelet syndrome is a rare, mostly autosomal recessive disorder of the megakaryocyte lineage. Patients present with macrothrombocytopenia, mild splenomegaly, increased serum vitamin B_{12}, and markedly decreased or absent platelet α-granules.

Storage pool deficiency and abnormalities of the granule secretion mechanism all result in malfunction of platelet secretion of substances required for platelet adhesion and aggregation.

Scott syndrome is characterized by the absence of calcium-stimulated transport of phosphatidylserine from the inner leaflet of the plasma membrane bilayer to the cell surface, which is required to provide an appropriate surface for the assembly of the complexes of the coagulation network. This results in moderately severe bleeding.

A variety of hereditary disorders may be associated with low platelet counts or platelets of abnormal size, including Wiskott–Aldrich syndrome.

The commonest acquired disorders of platelet function arise from drugs such as aspirin, nonsteroidal anti-inflammatory drugs, and ticlopidine. A wide range of other drugs may affect platelet function, including antihistamines, some antibiotics, antidepressants, and anesthetics. Platelet function may also be affected by chronic renal failure, the use of blood-bank platelets, leukemia, and cardiopulmonary bypass. In myelomatosis or macroglobulinemia, abnormal platelet function results from interference by circulating paraproteins, and bleeding may be readily controlled by plasmapheresis.

Disseminated Intravascular Coagulation

DIC is an acquired syndrome characterized by the intravascular activation of coagulation. It can originate from and cause damage to the microvasculature, which if sufficiently severe, may produce organ dysfunction. It is characterized by the unregulated generation of thrombin and the failure of the physiologic control mechanisms which normally keep a check on excess thrombin generation, and should be considered as indicating the presence of an underlying disorder. The coagulation system is activated by the rapid release of thromboplastic substances into the circulation to form either soluble or insoluble fibrin. Clotting factors and platelets are consumed, and there is defective and activated fibrinolysis and impairment of the coagulation inhibition system. The clinical syndromes result from vascular obstruction from fibrin-rich thrombi. Globules of fibrin are occasionally seen free in the circulating blood. Red blood cells are forced through fine networks of fibrin resulting in fragmentation, with the development of a microangiopathic hemolytic anemia. The overwhelming consumption of α_2-antiplasmin and platelets together with the anticoagulant properties of fibrin degradation products may also result in a bleeding tendency that can vary in severity from slight oozing at venepuncture sites with purpura and spontaneous bruising to massive uncontrollable hemorrhage (Fig. 25-5). Simultaneous hemorrhage and thrombosis may occur. Primary brain damage releases powerful thromboplastins into the circulation that may precipitate DIC, and all patients with evidence of brain injury are at risk for its development. DIC has been described in association with status epilepticus, possibly related to widespread endothelial injury secondary to seizure-induced hyperpyrexia.

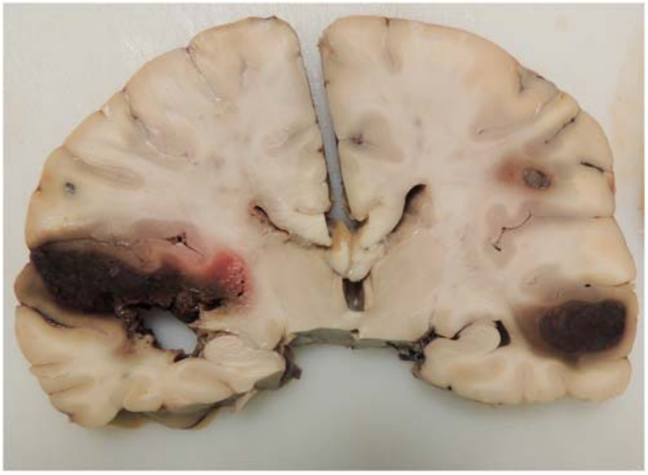

FIGURE 25-5 ■ Young male with promyelocytic acute myeloid leukemia complicated by DIC resulting in intracerebral and intraventricular hemorrhage.

The hemorrhagic complication may be so marked that massive cerebral, intraventricular, or subarachnoid hemorrhage occurs. When DIC affects the nervous system, the symptoms and signs are related to the thrombotic and hemorrhagic complications as well as to the primary disorder triggering the DIC (Table 25-2). Any part of the brain may be affected, producing focal or generalized encephalopathic manifestations. Symptoms and signs may fluctuate markedly with time, presumably because

TABLE 25-2 ■ **Clinical Conditions Complicated by Disseminated Intravascular Coagulation**

Mechanism	Clinical Condition
Tissue damage	Trauma (including neurotrauma), fat embolism
	Surgery
	Heat stroke
	Burns
	Dissecting aneurysm
	Neuroleptic malignant syndrome
	Pancreatitis
	Status epilepticus
Infection	Bacterial
	Viral
	Protozoal
	Rickettsial
Immunologic disturbance	Immune complex disorders
	Allograft rejection
	Incompatible blood transfusion
Obstetric complications	Abruptio placentae
	Amniotic fluid embolism
	Retained fetal products
	Eclampsia
Metabolic disorder	Diabetic ketoacidosis
Neoplasms	Myeloproliferative and lymphoproliferative disorders
	Mucin-secreting adenocarcinoma
Miscellaneous	Cyanotic congenital heart disease
	Hepatic failure
	Cavernous hemangioma
	Shock
	Snake venoms

of the continuing deposition and lysis of fibrin, which results in intermittent obstruction of vessels and blood flow. Patients may remain in a coma for several days and then make a good recovery if the circulation is reestablished.

In DIC secondary to carcinoma, microvascular obstruction of the brain may produce signs indistinguishable from those of metastatic deposits. Such signs may be found before clinical recognition of the underlying malignancy. Ischemic myelopathy due to DIC is rare.

No single test is available that is sufficiently sensitive or specific to permit a diagnosis of DIC. The presence of soluble fibrin in plasma has high sensitivity but low specificity for the diagnosis. The protamine sulfate test detects circulating fibrin monomers and is specific but not sensitive. The diagnosis frequently may be made using a combination of platelet count, measurement of global clotting times, measurement of one or two clotting factors and inhibitors (e.g., antithrombin), and a test for fibrin degradation products. Serial coagulation tests are often required and a reduced platelet count or a clear downward trend is a sensitive if not specific sign of DIC.

It is important to recognize coagulation syndromes that resemble DIC, especially thrombocytopenic purpura and fulminant antiphospholipid antibody syndrome. At the onset of the neurologic disorder in DIC, the coagulation profile may be normal. Plasma fibrinogen is an acute-phase reactant. During pregnancy, postoperatively, following trauma, and in association with malignancy it is invariably elevated so that increased fibrinogen consumption may serve only to reduce plasma fibrinogen to normal levels. For this reason, the only laboratory evidence of DIC in this situation may be thrombocytopenia and an elevated level of fibrin degradation products. The International Society on Thrombosis and Haemostasis has proposed a useful algorithm for the diagnosis of DIC.[8,9]

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a severe form of thrombotic microangiopathy resulting in organ failure of variable severity. The only consistent abnormalities are red cell fragmentation and thrombocytopenia, which are also found in other conditions. The condition results from excessive systemic platelet aggregation caused by the accumulation of unfolded high-molecular-weight von Willebrand factor multimers in plasma. The failure to degrade the multimers into less adhesive forms is related to a severe deficiency in a von Willebrand factor cleaving protease, ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). There are three types: (1) hereditary TTP, caused by mutations in *ADAMTS13* gene; (2) acquired idiopathic TTP, caused mainly by polyclonal IgG that inhibits plasma ADAMTS13 activity; and (3) acquired nonidiopathic TTP, which is associated with pregnancy, hematopoietic progenitor cell transplantation, infection, disseminated malignancy, and certain drugs such as ticlopidine and clopidogrel.

Severe deficiency of plasma ADAMTS13 activity or the presence of anti-ADAMTS13 autoantibodies is highly specific for the diagnosis. Treatments that eliminate anti-ADAMTS13 autoantibodies such as cyclosporine, cyclophosphamide, and rituximab are effective in treating acquired TTP.

TTP presents most commonly between the ages of 20 and 50 and affects women more commonly than men. Neurologic deficits may not be present, and the current diagnostic criteria no longer require the presence of renal and neurologic abnormalities or fever. Plasma exchange may therefore be introduced earlier, with a corresponding decline in the mortality rate. There may be complete recovery, but a chronic relapsing form has been described.

With the use of less restrictive diagnostic criteria, care must be taken to exclude conditions that may mimic TTP. These include DIC, disseminated malignancy, Evans syndrome (simultaneous or sequential development of autoimmune hemolytic anemia and immune thrombocytopenia with or without immune neutropenia), sepsis, accelerated hypertension, eclampsia, the catastrophic form of the antiphospholipid antibody syndrome, and HELLP syndrome (hemolysis, elevated liver function tests, low platelets), which is found in 10 percent of cases of eclampsia and pre-eclampsia. Unlike TTP, fetal involvement is present in the HELLP syndrome, with fetal thrombocytopenia reported in 30 percent of cases. In none of the mimics of TTP is there a reduction in ADAMTS13.

Pathologically, TTP is characterized by hyperplasia of endothelial and adventitial cells in arterioles, capillaries, and venules associated with platelet-rich and hyaline thrombi in these vessels, in which microaneurysms may also form.

Neurologic features are the most frequent presenting manifestations of TTP, occurring in 60 percent of cases. As the result of involvement of any part of the CNS, there is an endless variety of neurologic manifestations. Symptoms are typically transient and fluctuating and sometimes may resemble TIAs. Permanent neurologic complications may occur, and therefore neurologic symptoms should be treated vigorously with daily repeated plasma exchange, antiplatelet drugs, corticosteroids, and possibly chemotherapeutic agents such as vincristine.

The neurologic abnormalities in TTP may precede the full syndrome by months or even years. In a typical case, there may be a variety of nonspecific prodromal symptoms. At the time of presentation, the patient is usually pale, icteric, and febrile; has petechial hemorrhages in the skin; exhibits mental changes and neurologic abnormalities; and has splenomegaly, hepatomegaly, lymphadenopathy, arthropathy, and some degree of hypertension and renal insufficiency.

Posterior reversible encephalopathy syndrome is the most common brain imaging abnormality in severe TTP. The main laboratory abnormalities are microangiopathic hemolytic anemia, thrombocytopenia, hyperbilirubinemia, uremia, and erythroid and myeloid hyperplasia of the bone marrow with increased megakaryocytic activity. Although laboratory evidence of DIC may be present, it occurs in only a few patients. Demonstration of low levels ($\leq 5\%$) of normal ADAMTS13 is indicative of the diagnosis.

Treatment of acquired TTP consists of early plasma exchange to remove autoantibodies and ultralarge von Willebrand factor multimers and to replenish ADAMTS13. Caplacizumab, a humanized anti-von Willebrand factor immunoglobulin fragment, inhibits interaction between von Willebrand factor multimers and platelets and has an immediate effect on platelet aggregation and the ensuing formation and accumulation of platelet-rich microthrombi.

Hemolytic-Uremic Syndrome

The hemolytic-uremic syndrome (HUS) is characterized by renal impairment, thrombocytopenia, and microangiopathic hemolytic anemia, typically preceded by abdominal pain and diarrhea. Involvement of the nervous system is common. As with TTP, the diagnosis may be made on the basis of microangiopathic hemolytic anemia and thrombocytopenia, but there are important differences between the two entities. Deficiency of von Willebrand factor-cleaving protease has not been shown in HUS. Unlike TTP, 91 percent of children with HUS survive with only supportive care, and plasma exchange treatment is not indicated. Most cases arise as a complication of gastroenterologic infections by organisms producing Shiga toxins such as *Escherichia coli* O157:H7 or *Shigella.* Sporadic cases result from familial or autoimmune diseases, a variety of drugs (cyclosporine, mitomycin, and other forms of chemotherapy), tumors, bone marrow transplant, HIV infection, or are idiopathic.

Familial HUS constitutes 5 to 10 percent of cases. Several members of the alternative complement pathway are mutated in these patients, resulting in overactivation of the alternative pathway, either by losing regulatory functions or by gaining persistent or enhanced activation. Mutations in thrombomodulin, which regulates complement and the coagulation cascade, have also been described. There is thought to be a role for complement in diarrhea-associated HUS; Shiga toxin circulates bound to blood cells but not attached to Gb3 receptors. Instead, it binds to an as-yet undetermined receptor for which it has less affinity. Therefore, when the Shiga toxin finds its way to an organ which expresses Gb3, it preferentially detaches from circulating blood cells and binds to these receptors.

The most common neurologic manifestations are focal and generalized seizures. Behavioral changes, cerebral, cerebellar, and brainstem syndromes, and reversible cerebrovascular constriction syndrome have been described. Axonal neuropathy has been described in a patient with *E. coli* serotype O157:H7–associated HUS. Striatal involvement due to small areas of infarction, with resulting involuntary movements, may occur. MRI of the brain may show features of infarction or hemorrhage, and changes characteristic of posterior reversible encephalopathy syndrome are sometimes found. Patients in coma or with pyramidal signs may have normal imaging. In the German Shiga toxin-producing *E. coli* 0104:H4 outbreak, cognitive impairment, aphasia, and seizures were common but the outcome was good. There were no signs of microbleeds, thrombotic occlusions, or infarction. MR imaging and neuropathology seemed to indicate mixed toxic and inflammatory mechanisms. There is a risk of residual hypertension and chronic renal failure, which is greatest in those children with neurologic complications. Seizures, alone or as part of an encephalopathic illness, are associated with mortality or long-term neurologic sequelae.

There is increasing experience of the use of antibiotics, plasma exchange, and immunoabsorption, with the choice of therapy depending on the etiology. The recent use of eculizumab in the management of severe diarrhea-associated HUS has improved the outcome for patients with neurologic involvement.

Gaucher Disease

Gaucher disease is the most common lipid storage disorder, an autosomal recessive deficiency of glucocerebrosidase resulting in an accumulation of glucocerebroside in lipid-laden macrophages (Gaucher cells) in various organs. It is classified according to the presence of neurologic manifestations into three types: type 1, without neuropathic findings, type 2 with acute infantile neuropathic signs, and type 3, the chronic neuropathic form. More than 400 mutations have been identified accounting for the continuum of phenotypes. Patients with uniparental disomy or new mutations who do not inherit a mutation from each parent add to the complexity.

Type 1, resulting from accumulation in bones, liver, spleen, and lungs, is characterized by hepatosplenomegaly, bone pain and fractures, thrombocytopenia, and bleeding diathesis. It may develop at any time in childhood. It occurs worldwide in all populations, but 60 percent of cases are found in Ashkenazi Jews. Despite type 1 being considered a non-neuronopathic form, neurologic symptoms arise secondarily to skeletal disease, and cognitive impairment, developmental delay, microcephaly, behavioral disorder, mild spasticity, and polyneuropathy are described. Patients with type 1 Gaucher disease are predisposed to develop Parkinson disease.

Carriers of *GBA1* mutations with Parkinson disease are predisposed to particular motor and nonmotor features. Depending on the variant, this includes excessive daytime sleepiness, treatment-related wearing-off and dyskinesias, possible REM sleep behavior disorder, and motor and cognitive decline.[10]

Type 2, the acute neuronopathic form, shows no ethnic predilection. Hepatosplenomegaly arises in the first few months of life. Characteristic brainstem abnormalities then develop with strabismus, horizontal supranuclear palsy, opisthotonic posturing, and trismus arising in response to noxious stimuli. There is diffuse spasticity and developmental regression, and the disease is usually fatal during the first 3 years of life.

Type 3 Gaucher disease, the chronic neuronopathic form, is also without ethnic predilection and is estimated to occur in 1 in 50,000 live births. The neurologic symptoms are slowly progressive and appear later in childhood than the symptoms of type 2 disease. The disease has a more chronic course, with variable hepatosplenomegaly and the progressive development of incoordination, myoclonic seizures, impairment of olfaction, parkinsonian motor signs, pyramidal signs, cerebellar ataxia, and cranial nerve palsies. The cognitive disturbance ranges from a mild memory disorder to severe dementia, which is most frequent. Seizures may be tonic-clonic, focal with dyscognitive features, or myoclonic with prominent jerking of the face, limbs, or palate. Oculomotor apraxia has been described as the presenting feature. In addition, thrombocytopenia and prolonged prothrombin and partial thromboplastin times may cause bleeding. The patient may be anemic, and Gaucher cells may be found on bone marrow examination. Symptoms vary between individuals, so that some children have cirrhosis with portal hypertension, varices, pulmonary interstitial involvement, and heart disease. Type 3 Gaucher disease has been classified further as types 3a and 3b based on the extent of neurologic involvement and the presence of progressive myotonia and dementia (type 3a) or isolated supranuclear gaze palsy (type 3b).

Norbottnian Gaucher disease, a genetic form identified in Sweden, has features of types 2 and 3. The slowly progressive neurologic symptoms may not occur until early adulthood.

Treatment is through enzyme replacement and substrate reduction therapy. Studies on the effectiveness of therapy have used hemoglobin concentrations, platelet counts, reduction in spleen and liver volumes and parameters of bone disease as primary outcome measures, but rarely neurologic symptoms. Therapy has modified phenotypes of disease. The risk of skeletal disease or even multiple myeloma may be reduced or prevented but the effect on other complications is less clear. Enzyme replacement therapy with recombinant forms of macrophage-targeted acid β-glucosidase is beneficial for types 1 and 3 Gaucher disease, reducing liver and spleen size, improving blood counts, and reducing skeletal anomalies. It does not cross the blood–brain barrier and is therefore not effective in the management of neurologic symptoms. Substrate reduction therapy with *N*-butyl-deoxynojirimycin inhibits the enzyme glucosylceramide synthase, a glucosyl transferase responsible for the first step in the synthesis of glycosphingolipids. Unlike enzyme replacement therapy, this drug does cross the blood–brain barrier, but no data are yet available on whether it has a role in neuronopathic Gaucher disease.

Compounds that bind to and increase the stability of mutant enzymes are used as chaperones to increase the transfer of mutant enzyme from the endoplasmic reticulum to lysosomes. Their small molecular size means that they are able to cross the blood–brain barrier. Early studies of ambroxol, a mucolytic drug licensed as an expectorant, shows that it binds to mutant, misfolded glucocerebrosidase. Encouraging improvements in neurologic symptoms are reported.[11]

Bleeding and the New Anticoagulants

A number of new nonvitamin K antagonist oral anticoagulant drugs have been introduced in recent years. They act by direct thrombin or factor Xa inhibition, with the advantage of providing a stable level of anticoagulation on a regular dose, and do not require monitoring and dose adjustment as with warfarin.

Dabigatran, a direct thrombin inhibitor, is used for the prevention of stroke in patients with nonvalvular atrial fibrillation. When compared to people treated with warfarin, patients taking dabigatran have fewer life-threatening bleeds and fewer minor and major bleeds, including intracranial bleeds, but the rate of gastroenterologic bleeding is higher, mostly in patients over 75 years old. The most common side effect of dabigatran, seen in more than 10 percent of patients, is bleeding.

Idarucizumab, a humanized monoclonal antibody fragment, specifically binds to dabigatran with higher affinity than thrombin, rapidly neutralizing its anticoagulant effect without increasing the risk of thrombosis or controlling bleeding. In case reports it has been used successfully to reverse anticoagulation prior to the administration of intravenous recombinant tissue plasminogen activator (t-PA) thrombolysis for acute ischemic stroke.

Rivaroxaban and apixaban are highly selective direct inhibitors of factor Xa. They have been trialed successfully for postoperative thromboembolic prophylaxis and for the prevention of stroke associated with atrial fibrillation. The effects of these agents may be reversed by 4-factor prothrombin complex concentrate, and plasma exchange.

In comparison with warfarin, a very large retrospective study suggested that in patients with nonvalvular atrial fibrillation, apixaban was associated with lower risks of both stroke and major bleeding, dabigatran was associated with similar risk of stroke but lower risk of major bleeding, and rivaroxaban was associated with similar risks of both stroke and major bleeding.

COAGULATION DISORDERS

Thrombosis may arise from abnormalities of the blood-vessel wall, alterations in blood composition, and abnormalities in the dynamics of blood flow—the triad of Virchow. The intact vessel wall modulates thrombin activity, platelet reactivity, and the release of vasodilators, and it promotes local fibrinolytic activity. Injury of a vessel wall may therefore lead to the exposure of the prothrombotic subendothelium as well as interfere with its antithrombotic properties.

A number of blood components exhibit prothrombotic and antithrombotic effects, so that under normal circumstances platelet degranulation and aggregation as well as thrombin generation occur only at sites of tissue injury. Thrombin production is the major step in thrombosis that results in fibrin deposition. The fibrinolytic system prevents the deposition of excess fibrin, a negative-feedback process that is catalyzed by fibrin through plasmin production and also breaks down platelet-adhesive glycoproteins, further reducing platelet recruitment. The balance between prothrombotic and antithrombotic activity determines the degree of thrombus progression.

There are a number of well-recognized circumstances under which this balance may be altered. Tissue injury may lead to increased synthesis of plasminogen activator inhibitor type 1, with an increased risk of thrombosis. Congenital deficiencies of anticoagulant proteins are well recognized. Antiphospholipid antibodies are associated with venous and arterial thrombosis. Pregnancy is associated with a variety of changes in hemostatic components, giving rise to thrombosis or hemorrhage; increased fibrinogen production and placental production of a plasminogen activator inhibitor type 2 contribute to the increased risk of thrombosis in the later stages of pregnancy. Cigarette smoking, estrogen use, tissue injury, infection, and inflammation each result in increased production of components of the cascade, particularly fibrinogen.

Diminished blood flow may lead to the local accumulation of platelets and thrombin, and, if the stasis is sufficient, endothelial hypoxia may result in impairment of the antithrombotic properties of the endothelium. Blood viscosity is a significant determinant of blood flow. Under low-flow conditions, platelets have only a minor role in the generation of thrombosis; stasis is the dominant factor in the pathogenesis of venous thrombosis in which activated clotting factors circulate to areas of venous stasis, where fibrin is generated. This process is exacerbated by defects in innate anticoagulant mechanisms. In the arterial system, thrombosis usually arises from endothelial damage, commonly in association with atherosclerosis. Procoagulant mechanisms may be involved in the initiation and progression of atherosclerosis, but local platelet degranulation results in plaque growth. Plaque rupture or ulceration is often the final event that exposes procoagulant material with rapid formation of platelet thrombus, which may break up and embolize or become consolidated and enlarged by fibrin deposition.

It follows from the physiology of thrombosis that differing risk factors are responsible for the generation of venous and arterial thrombosis. Furthermore, the multifactorial nature of thrombophilia is becoming increasingly apparent, and individuals with more than one inherited thrombophilia risk factor or those with an inherited and an acquired risk factor are particularly prone to thrombosis.

Routine evaluation for hypercoagulability, such as assays for deficiencies of coagulation inhibitors or genetic analysis for the factor V Leiden or prothrombin 20210 mutation, is not helpful in identifying risk factors for adult patients with stroke, other than in the context of an associated systemic venous clot that may travel through a right-to-left shunt, such as a patent foramen ovale.

Antiphospholipid Antibodies

The lupus anticoagulant and anticardiolipin are members of a group of antiphospholipid antibodies that are associated with venous and, to a lesser degree, arterial thrombosis. A diagnosis of antiphospholipid syndrome requires the combination of at least one clinical and one laboratory criterion which is persistent over time. Anticardiolipin and anti-β_2-glycoprotein I antibodies, detected by the use of enzyme-linked immunosorbent assay, and the lupus anticoagulant, detected by clotting assays, are the recommended tests for the syndrome. Antiphospholipid antibodies comprise a family of antibodies that react with serum phospholipid-binding plasma proteins, among which β_2-glycoprotein I (GPI) is the most important. This results in endothelial nitric oxide synthase antagonism via apolipoprotein E receptor 2–dependent processes.

Antibodies to protein S, protein C, prothrombin, annexin V, and annexin II have also been described. Affinity for coagulation-active negatively charged lipids is the basis for phospholipid-dependent coagulation assays for lupus anticoagulant.

In SLE, predisposition to thrombosis is associated with the presence of antinuclear antibodies and antiphospholipid antibodies. The primary antiphospholipid syndrome is the association between arterial and venous thrombosis with the lupus anticoagulant, anticardiolipin, or other phospholipid antibodies, along with a history of recurrent early miscarriage and sometimes thrombocytopenia, in the absence of SLE or other connective tissue disorders. In a cohort of 1,000 patients with the antiphospholipid syndrome, 82 percent were female, primary antiphospholipid syndrome was present in 53 percent, and SLE was associated in 36 percent. Antiphospholipid antibodies may arise de novo or may be associated with a variety of underlying disorders, as discussed in Chapters 11 and 50. The risk of thrombosis is variable; antiphospholipid antibodies associated with infections and a variety of drugs are associated with a smaller risk of thrombosis than those of primary or secondary antiphospholipid syndromes. The presence of more than one class of antiphospholipid antibody increases thrombotic risk. Patients with triple positivity (anticardiolipin, the lupus anticoagulant, and anti-β_2-glycoprotein 1) have a 30 percent chance of thrombosis even when anticoagulated.

Since patients with clinical manifestations may have multiple antiphospholipid antibodies, testing must include at least two sensitive coagulation assays, usually the kaolin-cephalin clotting time (KCCT) and the dilute Russell viper venom time

(DRVVT) with a platelet neutralization step, as well as the solid-phase assays for IgG and IgM anticardiolipin antibody. Long kaolin-cephalin clotting times may arise from coagulation factor deficiency, and false-negative antiphospholipid antibody testing may occur from binding of the antibodies to platelets in samples not processed rapidly and appropriately. Low-titer antibodies and IgM antibodies are most likely to be nonpathogenic. Transient positive antibodies, particularly IgM, may follow a variety of infections, so positive tests should be repeated after at least 12 weeks as in the current revised Sapporo classification criteria.[12]

Isolated anti-β_2-GPI antibodies are not associated with thrombosis. The combination of the IgG anti-β_2GPI domain I antibody and IgG/IgM antiphosphatidylserine/prothrombin complex antibody tests shows a high positive predictive value for the diagnosis of antiphospholipid syndrome.

Annexin V is a natural anticoagulant with a high calcium-dependent binding affinity for negatively charged phospholipids that acts competitively with coagulation factors to inhibit the prothrombin complex. High levels of antiannexin V antibodies have been found in 20 to 30 percent of patients with SLE. There is growing evidence that the antiphospholipid antibody-mediated disruption of the annexin V anticoagulant crystal shield is a mechanism for pregnancy losses and thrombosis in patients with antiphospholipid syndrome. There is early evidence that annexin antibodies may relate to clinical manifestations in SLE and with the course of the disease in Behçet disease.

Depression, cognitive dysfunction, psychosis, seizures, chorea, and transverse myelitis have been associated with the presence of antibodies, although there is evidence that not all arise from ischemia. Neuropsychiatric lupus manifestations, especially the common disorders of mood and cognition, may be mediated by cytokines or by antibodies. A subset of anti-DNA antibodies binds the NMDA receptor. High titers are present in 30 to 40 percent of SLE patients and are associated with cognitive impairment.

Sneddon syndrome is a noninflammatory thrombotic arteriopathy affecting medium- and small-sized arteries, characterized by the combination of multiple cerebral infarcts and livedo reticularis. It may be idiopathic or associated with a primary antiphospholipid syndrome or with SLE with or without antiphospholipid syndrome.

Epilepsy occurs in 8.6 percent of patients with the antiphospholipid syndrome. Multivariate logistic regression analysis identified CNS thromboembolic events as the most significant risk factor for epilepsy in these patients, with an odds ratio (OR) of 4.1, followed by SLE (OR 1.4) and valvular vegetations (OR 2.9).

The clinical features have been described in 1,000 patients with antiphospholipid syndrome. Neurologic manifestations include migraine (20.2%), stroke (19.8%), TIA (11.1%), epilepsy (7.0%), amaurosis fugax (5.4%), vascular dementia (2.5%), retinal artery thrombosis (1.5%), chorea (1.3%), acute encephalopathy (1.1%), optic neuropathy (1.0%), retinal vein thrombosis (0.9%), transient amnesia (0.7%), cerebral venous sinus thrombosis (0.7%), cerebellar ataxia (0.7%), transverse myelopathy (0.4%), and hemiballismus (0.3%).

Many studies have examined the association between antiphospholipid antibodies and stroke. A study of unselected adults presenting with stroke suggested that the presence of anticardiolipin antibodies is an independent risk factor for stroke but does not predispose to subsequent thrombotic events. The Antiphospholipid Antibodies and Stroke Study (APASS), a prospective cohort study within the Warfarin vs Aspirin Recurrent Stroke Study (WARSS), did not predict an increased risk for subsequent vascular occlusive events over 2 years. Routine screening for antiphospholipid antibodies in unselected adults with ischemic stroke is therefore not recommended. With the introduction of assays for antibodies directed specifically against β_2-glycoprotein I, however, a relative risk of 2 to 3 for stroke has been suggested. Studies of a wider range of antiphospholipid antibodies in the pathogenesis of cerebral ischemia suggest a relevant role for a combination of antiphosphatidylserine IgG and anti-β_2-glycoprotein-I IgA in stroke etiology.

Among younger patients, the association appears stronger, with antiphospholipid antibodies present in 46 percent of patients younger than 50 years who present with stroke or TIA compared with 8 percent of matched control subjects with nonthrombotic neurologic disease. In young adults, the presence of antiphospholipid antibodies, particularly the lupus anticoagulant, has been identified as an independent risk factor for first and possibly also for recurrent ischemic stroke, although a prospective study of young patients with recent TIA or ischemic stroke failed to show that antiphospholipid antibodies are a strong risk factor for recurrent stroke or TIA. Isolated IgM antiphospholipid syndrome patients represent 14.3 percent of the antiphospholipid syndrome population. They are older at diagnosis and have a significantly increased risk of stroke.

Hereditary Thrombophilia

The inherited thrombophilias are a group of disorders in which a defect or deficiency in the natural anticoagulant mechanisms predisposes to the development of venous thrombosis. Investigation into potentially inherited disorders must include assessment of family members.

Within the cerebral venous sinuses, the superior sagittal and transverse sinuses are frequently involved, whereas cavernous sinus thrombosis is much less common. Antithrombin III, protein C, and protein S deficiencies, factor V Leiden mutations, the prothrombin G20210A gene mutation, and *MTHFR* C677T mutations (resulting in hyperhomocysteinemia) all predispose to thrombosis. Other inherited disorders, such as deficiency of heparin cofactor 2, plasminogen, t-PA, factor XII, or prekallikrein may result in a modestly increased risk of thrombosis.

The genetic risk factors for venous thrombosis can be categorized by their level of increased risk. Strong risk factors include deficiencies of antithrombin III, protein C, and protein S, which collectively affect less than 1 percent of the population. Because these deficiencies are rare, most reports on risk come from family studies, which suggest that these deficiencies can lead to highly penetrant phenotypes with a 10-fold risk for heterozygote carriers. Studies from unselected consecutive patients, however, indicate that the risks are much less, raising the possibility that these families may carry other unrecognized defects. Moderately strong risk factors for thrombosis are the factor V Leiden mutation, prothrombin 20210A mutations, non-O blood group mutations, and the fibrinogen 10034 T mutation. There are many weak genetic risk factors identified, including fibrinogen, factor XIII, and factor XI variants. Even for moderately strong risk factors (relative risks 2 to 5), the majority of carriers will never develop thrombosis.

A large genome-wide association study suggested that common variants could explain about 35 percent of venous thrombosis susceptibility, of which only 3 percent could be attributable to the main identified genes. The relevance of the findings to cerebral venous thrombosis remains unclear.

The combined retrospective and prospective multicenter VENOST study of Cerebral Venous Thrombosis in Caucasian patients studied 1,144 patients. In 26.4 percent, prothrombotic conditions were identified, with 19 percent having more than one cause identified. These causes included *MTHFR* (methylenetetrahydrofolate reductase) homozygote mutation in 6.3 percent and heterozygote mutation in 5.1 percent. Factor V Leiden homozygote mutation occurred in 5.1 percent, prothrombin gene mutation in 2.6 percent, PAI mutation in 1.4 percent, protein C or S deficiency in 5.0 percent, hyperhomocysteinemia in 4.8 percent, activated protein C resistance in 1.5 percent, and antithrombin III deficiency in 0.5 percent.

Antithrombin III Deficiency

Antithrombin is a plasma glycoprotein that inhibits thrombin and other activated serine proteases, including factors IXa, Xa, XIa, XIIa, and kallikrein. Heterozygous antithrombin III deficiency affects 1 in 2,000 to 5,000 of the population and may arise as a new mutation. Deficiency is associated with sagittal sinus and other cerebral venous sinus thromboses. A more rare disorder is recognized in which a nonsense mutation results in a dysfunctional variant of antithrombin causing recurrent venous thrombosis. Acquired antithrombin III deficiency associated with cerebral venous sinus thrombosis may also arise from reduced antithrombin synthesis due to liver disease or increased loss in nephrotic syndrome, oral contraceptive use, DIC, protein malnutrition, and heparin therapy. A retrospective cohort family study that assessed the risk of venous thromboembolism in individuals with thrombophilia suggested that antithrombin III deficiency may be associated with a higher risk of thrombosis than the other genetic defects.

Protein C Deficiency

Cerebral venous sinus thrombosis is associated with deficiency of protein C, which is a vitamin

K–dependent protein that binds to thrombomodulin, an endothelial cell surface protein, and is converted to an active protease by the action of thrombin. In conjunction with protein S, protein C proteolyses factors Va and VIIIa, thereby reducing thrombin formation and promoting fibrinolysis. Inheritance of protein C deficiency is usually autosomal dominant, although in some families heterozygotes with plasma concentrations of less than 50 percent of normal remain asymptomatic, giving an autosomal recessive–like pattern of inheritance. Dysfunctional molecules that are present in normal levels are described.

Population studies suggest that 1 in 200 to 300 subjects have levels of protein C consistent with congenital deficiency, although the incidence of protein C deficiency and venous thromboembolism suggests a prevalence of 1 in 30,000. This represents 4 percent of subjects with venous thromboembolism presenting before the age of 45 and demonstrates that other inherited and acquired risk factors are frequently required for thrombosis to occur.

PROTEIN S DEFICIENCY

Sagittal sinus and other cerebral venous sinus thromboses are reported in association with deficiency of protein S, which is a vitamin K-dependent glycoprotein that acts as a cofactor for activated protein C. Approximately 60 percent of protein S is protein bound, so that total and free levels must be measured. Only the unbound protein is biologically active, and since its level may fall in acute disease, repeat measurement and the demonstration of a persistently reduced level are required to prove association. Acquired protein S deficiency has been identified in hepatic disease, vitamin K deficiency, pregnancy, and hormonal contraceptive use. In the presence of the factor V Leiden mutation, functional assays of protein S may give a falsely low reading.

FACTOR V LEIDEN (RQ506Q)

The factor V Leiden mutation is a common gain-of-function mutation in factor V at Arg 506. Protein C cleaves and inactivates the Va procoagulant, resulting in factor V Leiden becoming resistant to inactivation by activated protein C. Factor V Leiden is the most commonly inherited prothrombotic state, accounting for at least 90 percent of the cases of resistance to activated protein C. The mutation is inherited as an autosomal dominant trait and has a prevalence of approximately 5 percent in the Caucasian population. It is found in 20 percent of patients with venous thrombosis and approximately 50 percent with familial thrombophilia. A number of clinical studies, using different inclusion criteria, show a prevalence of activated protein C resistance ranging from 20 to 60 percent among patients with venous thromboembolism at any site, and 20 to 25 percent in cerebral venous sinus thrombosis. The actual thrombotic risk is moderate, but its high prevalence makes it by far the most important inherited risk factor. The risk appears to be greatest in neonates and children.

Acquired activated protein C resistance, not due to the factor V Leiden mutation, is also a risk factor for venous thrombosis. Thrombotic events often occur in the presence of noninherited risk factors (e.g., oral contraceptive intake, pregnancy, puerperium, trauma, or prolonged immobilization) which are also present in many cases of cerebral venous sinus thrombosis with the factor V Leiden mutation.

PROTHROMBIN G:A 20210 MUTATION

Prothrombin is a precursor of the serine protease thrombin, a key enzyme in the production of fibrin from fibrinogen. A single nucleotide substitution (G to A) at position 20210 is associated with an increased risk of deep venous thrombosis and cerebral venous sinus thrombosis. Carriers have a two- to threefold increased risk of venous thrombosis at any site, and the variant is found in approximately 6 percent of patients with venous thrombosis. The mutation is found in 18 percent of selected patients with a family history of venous thrombosis, and 1 to 2 percent of control subjects, making it the second most common cause of hereditary thrombophilia after the factor V Leiden mutation. The prevalence of the prothrombin gene mutation is 20 percent in patients with cerebral venous sinus thrombosis in comparison with 3 percent of healthy control subjects. The prevalence of this mutation varies, contributing to cerebral venous thrombosis in European and South American populations but apparently not in the Middle East and East Africa.

Hyperhomocysteinemia

Meta-analyses have been reported as showing an increased risk of venous thromboembolism of two- to threefold in hyperhomocysteinemia. However, after extensive adjustments for confounding factors, no association with an increased risk of venous thrombosis has been shown.

A C-to-T mutation at position 677 in the methylene tetrahydrofolate reductase gene (*MTHFR*) gives rise to a thermolabile variant with reduced activity accompanied by elevated plasma homocysteine. Homozygosity for the thermolabile form is found in 5 to 15 percent of the general population who have significantly elevated plasma homocysteine levels.

Moderate hyperhomocysteinemia is now recognized as a risk factor for arterial disease, including carotid artery stenosis and stroke. It has also been suggested that hyperhomocysteinemia plays a role in the development of small-vessel ischemia. Further discussion of hyperhomocysteinemia is provided in Chapter 11.

Factor VIII

The levels of the procoagulant factor VIII are associated with an increased risk of arterial and venous thrombosis. High factor VIII levels appear particularly to be a risk factor for thrombosis in children. The MEGA follow-up study demonstrated a strong predictive value of factor VIII levels with a dose-response such that those with the highest levels have a triple risk of recurrent thrombosis compared with those with lower levels. In patients with a first venous thrombosis, the risk of recurrence is not high enough to outweigh the bleeding risk associated with continued anticoagulant treatment.

Interactions Between Inherited Thrombophilias

The multifactorial nature of thrombophilia is well-recognized. Among 162 patients and 336 control subjects, two or more polymorphisms were detected in 16.7 percent of patients and 0.9 percent of controls. The odds ratios for venous thrombosis with the joint occurrence of the factor V Leiden and prothrombin G20210A mutations was 58.6; for the factor V Leiden mutation and *MTHFR* polymorphisms was 35.0; and for the prothrombin G20210A mutation and *MTHFR* polymorphisms was 7.7. Coexistence of additional antithrombin III, protein C, or protein S deficiency has been reported in 14.5 percent of patients with the factor V Leiden mutation. As factor V Leiden and prothrombin 20210A mutations are both common, compound heterozygotes are not particularly rare and have a 20-fold increased risk of thrombosis; this combination of thrombophilias is associated with an increase in the prevalence of more unusual sites of venous thrombosis, such as the cerebral venous sinuses.

Thrombophilic Disorders and Arterial Thrombosis

Although there are numerous reports of cerebral arterial thrombosis and infarction occurring in antithrombin III, protein C, and protein S deficiencies, as well as with factor V Leiden mutations, the risk is extremely small compared with the risk of venous thrombosis. The prospectively conducted FUTURE study showed that prothrombotic factors do not increase the risk of recurrent ischemic events after cryptogenic stroke at young age. A stroke in the presence of a strong risk factor for venous thrombosis should therefore always raise the suspicion of paradoxical venous embolism.

Only rarely has familial thrombophilia been diagnosed conclusively following arterial thrombosis, by demonstrating that the deficiency persists after the acute event is over. This is particularly important in the case of protein S, since it binds to an acute-phase reactant (C4bBP), resulting in an acquired reduction in free or functional protein S. Low protein S levels are also found in acute nonvascular illness and during pregnancy, and protein C levels may fall in liver disease, postoperatively, and in association with DIC. Serial protein C measurements demonstrate that it may take 3 months for levels to return to normal following a stroke. Case-control studies have failed to identify an association between factor V Leiden and arterial stroke.

In interpreting the reports suggesting that hereditary thrombophilia may be associated with stroke in childhood, it should be noted that reference ranges are lower than for adults, so the association may be erroneous. Ethnic differences have also been noted in the levels of markers of thrombophilia in stroke, emphasizing the need for care in interpreting these tests.

Interactions between genetic and noninherited risk factors, particularly oral contraceptives, should be considered, although progesterone-only contraceptives do not add to risks of thrombosis. Any association between the inherited thrombophilias and arterial stroke is therefore weak and is likely to be enhanced by other prothrombotic risk factors.

Patent Foramen Ovale

In patients 55 years or younger with cryptogenic (presumed embolic) stroke, patent foramen ovale has been shown to be a more common finding (56%) than in controls (18%) and in those patients with stroke of undetermined cause (17%). An association has been shown between the presence of coagulation abnormalities, especially the factor V Leiden and prothrombin G20210A mutations, and a history of Valsalva maneuver-like activity at stroke onset. Such activity was more common at stroke onset in patients with, rather than without, patent foramen ovale, suggesting paradoxical embolism as a mechanism. Coagulation abnormalities have been found in 30 percent of patients with cryptogenic infarction who also had patent foramen ovale; however, the combined presence of patent foramen ovale and antiphospholipid syndrome does not increase the risk of subsequent cerebrovascular events. Interestingly, the prevalence of prothrombin mutations is higher in patients with a patent foramen ovale as compared to stroke patients without a patent foramen ovale, raising the possibility that there may be an association between the coagulopathy and the formation of intracardiac shunts. No significant association was found between the *MTHFR* genotype and strokes related to patent foramen ovale. With the introduction of devices to close patent foramen ovale percutaneously, the risks of closure has fallen. A meta-analysis of five studies though with some heterogeneity of medical treatment and nature of the patent foramen ovale, suggests that closure is superior to medical therapy for reducing stroke risk in patients with cryptogenic stroke.

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CHAPTER

26

Metastatic Disease and the Nervous System

JASMIN JO ■ DAVID SCHIFF

METASTASES TO THE CENTRAL NERVOUS SYSTEM AND RELATED STRUCTURES
- Brain
  - *Epidemiology*
  - *Pathophysiology*
  - *Pathology*
  - *Clinical Features*
  - *Diagnostic Studies*
  - *Differential Diagnosis*
  - *Prognostic Variables*
  - *Treatment*
- Skull Base
  - *Definition and Epidemiology*
  - *Pathophysiology*
  - *Clinical Features*
  - *Diagnostic Studies*
  - *Differential Diagnosis*
  - *Treatment*
  - *Prognosis*
- Intracranial Dura
  - *Definition and Epidemiology*
  - *Pathophysiology*
  - *Clinical Features*
  - *Diagnostic Studies and Differential Diagnosis*
  - *Treatment*
  - *Prognosis*
- Spine and Spinal Cord
  - *Epidemiology*
  - *Classification by Anatomic Location*
  - *Epidural Spinal Cord Compression*
  - *Intramedullary Spinal Cord Metastases*
- Leptomeninges
  - *Definition*
  - *Epidemiology*
  - *Pathophysiology*
  - *Clinical Features*
  - *Diagnostic Studies*
  - *Treatment*
  - *Prognosis*

METASTASES TO THE PERIPHERAL NERVOUS SYSTEM
- Plexuses
  - *Definition and Epidemiology*
  - *Pathophysiology*
  - *Anatomic Considerations and Clinical Features*
  - *Diagnostic Studies*
  - *Differential Diagnosis*
  - *Treatment and Prognosis*
- Peripheral Nerves
  - *Definition and Epidemiology*
  - *Mechanisms, Clinical Features, and Diagnosis*
  - *Treatment and Prognosis*

METASTASES TO MUSCLES
- Epidemiology and Pathophysiology
- Clinical Features
- Diagnostic Studies
- Differential Diagnosis
- Treatment and Prognosis

CONCLUDING COMMENTS

The entire nervous system is potentially vulnerable to metastatic disease, typically occurring in the setting of a known disseminated systemic malignancy. Approximately 45 percent of patients with systemic cancer and neurologic deficits are found to have metastatic involvement of the nervous system. The most common cancer-related neurologic diagnosis is brain metastasis (16%), followed by bone metastasis (10%) and epidural metastasis (9%). The incidence of metastatic involvement of the nervous system continues to rise due to improved treatment strategies directed toward primary cancers and systemic metastases. In 2019, estimated new cancer cases in the United States exceeded 1.7 million.[1]

Metastatic involvement of the central nervous system, including its overlying structures, and the peripheral nervous system causes significant neurologic morbidity and mortality. The skeletal muscles are

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affected only rarely. Early diagnosis and treatment may prevent disability in these groups of patients, most of whom have a limited life expectancy.

METASTASES TO THE CENTRAL NERVOUS SYSTEM AND RELATED STRUCTURES

Brain

EPIDEMIOLOGY

In the United States between 2010 and 2013, 217,687 out of 1.3 million patients with malignancy were diagnosed with one or more metastases. A total of 26,430 patients, 2 percent of all patients with cancer and 12.1 percent of those with metastatic disease, were found to have brain metastases at diagnosis. The estimated incidence of identified brain metastases among patients with newly diagnosed cancer is 23,598 annually. Patients with small cell and nonsmall cell lung cancer have the highest rate of brain metastasis at the time of cancer diagnosis. Among patients with metastatic disease, patients with melanoma (28.2%), lung adenocarcinoma (26.8%), nonsmall cell lung cancer not otherwise specified/other lung cancer (25.6%), small cell lung cancer (23.5%), squamous cell lung carcinoma (15.9%), bronchioloalveolar carcinoma (15.5%), and renal cancer (10.8%) have the highest incidence proportion of brain metastases.[2] Brain metastases are more common in Hispanics or Asians than other ethnic groups. The incidence of brain metastasis is increasing and this has been related to improvements in systemic therapy and to greater utilization of appropriate imaging studies.

PATHOPHYSIOLOGY

The most common mechanism of spread to the brain is hematogenous dissemination. The "anatomic or mechanical" hypothesis states that the distribution of metastases is related to the amount of blood flow to the brain. This phenomenon explains the predilection for brain metastases to involve the cerebral hemisphere in 80 percent, cerebellum in 15 percent, and brainstem in 5 percent of cases. As cancer cells travel through the arterial circulation, they become trapped in the end arteries at the gray–white matter junction (Fig. 26-1). Only about two-thirds of metastases can be explained by blood flow alone, suggesting that other factors play a role. The "seed and soil" mechanism postulates that appropriate tumor cells or "seeds" grow in site-specific hosts or "soil." Brain metastases are hypothesized to result from neurotropic factors facilitating "brain-homing" and direct interaction with neural substance. The vascular basement membrane of pre-existing blood vessels promotes nonsprouting angiogenesis and proliferation of metastatic tumor cells by means of tumor cell vascular endothelial growth factor (VEGF).

Clinical studies have detected specific genomic mutations present in brain metastases, but not in the primary tumor or in extracranial metastases. In a comprehensive genomic study of matched brain metastases, primary tumors, and normal tissues, over 50 percent of brain metastases had additional targetable mutations that were not found in the matched clinically sampled primary tumors.[3] These additional oncogenic alterations may have driven the proliferation or survival of a prometastatic subclone within the primary tumor, leading to metastases. Contiguous brain invasion from intracranial dural and skull-base metastases is another mechanism by which brain metastases occur.[4]

PATHOLOGY

Grossly, metastatic tumors in the brain are well-circumscribed and surrounded by edematous white matter; cystic degeneration, necrosis, and hemorrhage can be seen. Metastatic lesions from melanoma, choriocarcinoma, and renal cell carcinoma have a high tendency for intratumoral hemorrhage. Microscopically, brain metastases are usually well-demarcated and generally appear histologically similar to the primary tumor. Vascular proliferation within the lesions and reactive astrocytosis in the surrounding brain parenchyma may be encountered. Metastases from breast, kidney, and colon are usually solitary, whereas multiple metastases are common from melanoma and lung carcinoma. Molecular genetic analysis can provide information in determining metastatic cancers of unknown origin. Molecular studies also define oncogenic pathways such as in lung cancer (ALK, C-MET, ROS1, RET), breast cancer (Her2/Neu), and melanoma (BRAFV600E, NRAS, CKIT) that can be targeted for therapy.[4]

CLINICAL FEATURES

Neurologic manifestations in patients with brain metastases may be focal, resulting from local displacement or

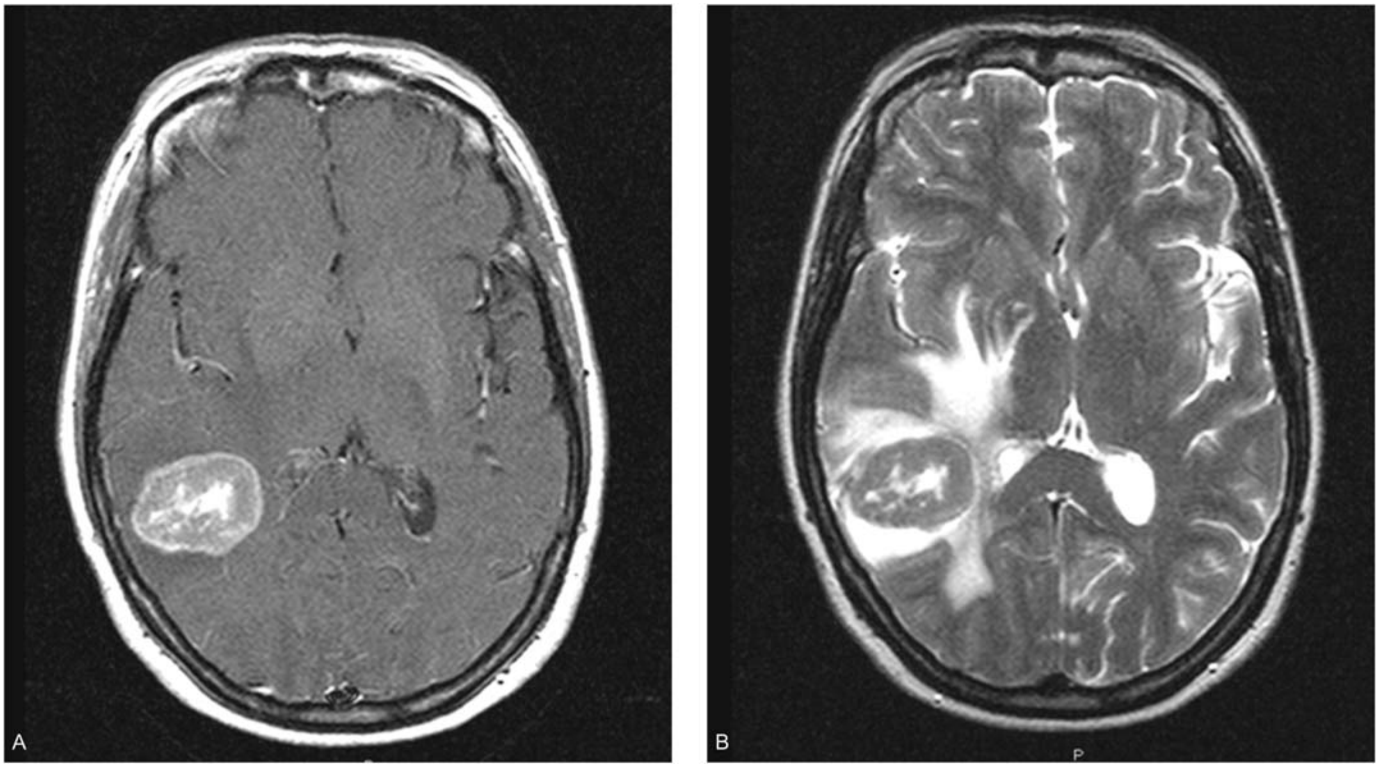

FIGURE 26-1 ■ Solitary brain metastasis in a patient with breast carcinoma. *A*, Postcontrast T1-weighted gadolinium magnetic resonance imaging (MRI) sequence demonstrating peripheral and central enhancement of a mass in the right posterior temporal lobe; *B*, T2-weighted MRI sequence demonstrates a large field of high signal with finger-like projections in the white matter extending anteriorly within the temporal lobe and posteriorly within the parietal lobe, consistent with vasogenic edema.

destruction of the surrounding parenchyma by the tumor or edema, or generalized due to increased intracranial pressure (ICP) or hydrocephalus. Patients usually present with subacute or chronic progressive neurologic signs and symptoms. Headache, typically worse in the morning, is the most common presenting symptom, affecting approximately 50 percent of patients. Focal neurologic deficits are present in 30 to 40 percent of patients, cognitive dysfunction in 30 to 35 percent, and seizures as a presenting feature in 15 to 20 percent. Another 5 to 10 percent of patients present with acute "stroke-like" symptoms due to intratumoral hemorrhage. Nearly 15 percent are asymptomatic.

Over 80 percent of patients diagnosed with brain metastases have a known systemic malignancy (metachronous presentation). In up to 30 percent of patients, brain metastases are diagnosed at the same time as the primary malignancy (synchronous presentation) and in another 5 to 10 percent the brain metastases are the presenting manifestation (precocious presentation). A majority of patients (more than 30%) have multiple metastases with more than four lesions, 20 to 30 percent have two to three lesions ("oligometastases"), and another 20 to 30 percent have a solitary metastasis.[4,5]

DIAGNOSTIC STUDIES

Magnetic resonance imaging (MRI) is the diagnostic modality of choice for the evaluation and monitoring of patients with brain metastases and is much more sensitive than computed tomography (CT) in detecting the number, size, location, and secondary effects of the lesions. Brain metastases tend to be multiple, spherical, and located at the gray–white matter junction, with surrounding vasogenic edema. These lesions appear isointense or hypointense on precontrast T1-weighted MRI sequences and enhance avidly upon contrast administration due to a disrupted blood–brain barrier. The surrounding edema is hyperintense on T2-weighted and fluid-attenuated inversion recovery sequences (Fig. 26-1). The amount of surrounding edema is often disproportionate to the size of the lesions. Intratumoral hemorrhage within the tumor, when present, is evident on precontrast T1 and gradient

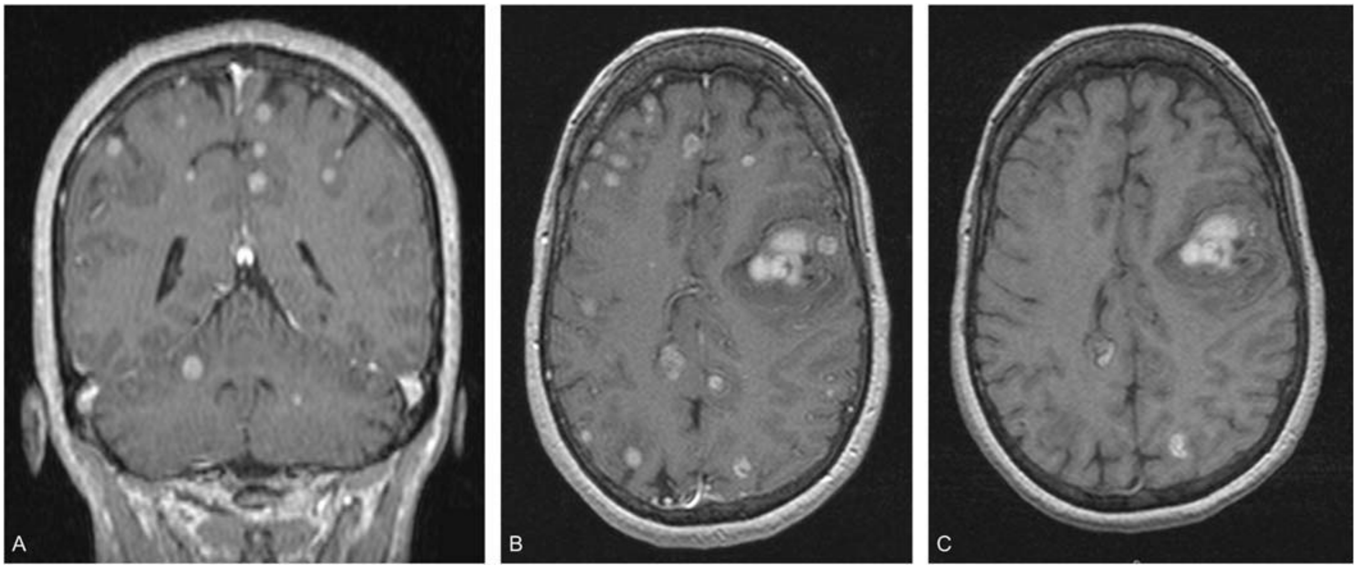

FIGURE 26-2 ■ Multiple metastases with intratumoral hemorrhage from metastatic melanoma. *A* and *B*, Numerous contrast-enhancing lesions are present on T1-weighted postcontrast MR images of the supratentorial and infratentorial brain. *C*, Several lesions are present, the largest in the left frontal lobe, and show T1 shortening consistent with the presence of blood, with surrounding edema resulting in midline shift towards the contralateral side.

recalled echo sequencing (Fig. 26-2). CT studies are generally utilized in acute settings to determine the presence of hemorrhage, herniation, or hydrocephalus. For patients previously treated with radiation, the differentiation of tumor recurrence from radiation effects with routine MRI may be challenging. Increased glucose metabolism with [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) studies is characteristic for brain metastases, whereas lesions composed of radiation necrosis are frequently hypometabolic. Increase in relative cerebral blood volume on MR perfusion imaging may also allow this distinction. MR spectroscopy often shows lower choline-to-creatinine ratio in brain metastases than in high-grade gliomas.[4,5]

A search for primary malignancy should be performed in patients with suspected brain metastases without a known systemic cancer. CT of the chest takes precedence over abdominal and pelvic evaluation because of the high frequency of brain metastases originating from the lungs. Whole-body FDG-PET is also helpful in investigating the primary source, although it has low specificity in differentiating malignant from benign inflammatory lesions. Biopsy of tumors discovered upon systemic evaluation is often easier than biopsy or resection of the brain lesion.[4,5]

DIFFERENTIAL DIAGNOSIS

Several conditions mimic the radiologic findings of brain metastases including high-grade glioma, lymphoma, abscess, stroke, and demyelinating disorders. Different imaging techniques and special characteristics of the lesions may help distinguish between these clinical entities. An elevated cerebral blood volume in perfusion studies reflects tumor vascularity and is diminished in edema, radiation necrosis, or infarct. MR spectroscopy detects the metabolic characteristics of these lesions, differentiating spectra of metastases, gliomas, vasogenic edema, or gliosis, and other mass lesions. Diffusion-weighted imaging (DWI) detects areas of the brain with decreased proton mobility, while the apparent diffusion coefficient (ADC) characterizes the rate of diffusional motion; unrestricted diffusion in DWI and high ADC value in the center of a ring-enhancing mass are suggestive of a necrotic mass as seen in metastasis or high-grade glioma. Restricted diffusion represents cytotoxic edema in an acute infarct, and is also seen in highly cellular lesions such as cerebral abscess, infectious encephalitis, or primary CNS lymphoma. In many cases, brain biopsy is required for definitive diagnosis.

PROGNOSTIC VARIABLES

Classifying patients with brain metastases based on prognosis helps clinicians maximize survival while avoiding unnecessary treatments. Important factors that predict outcomes are age, performance status, status of primary tumor, and extent of extracranial disease. The Radiation Therapy Oncology Group used recursive partitioning analysis (RPA) to categorize patients into three prognostic classes. Patients harboring all four favorable prognostic factors [age less than 65 years, Karnofsky performance status (KPS) of at least 70, controlled primary tumor, and no extracranial metastases] had the best prognosis, with expected median survival of 7.1 months. Patients with KPS of 70 or more but at least one other unfavorable factor have an intermediate prognosis, with expected median survival of 4.2 months. A KPS of less than 70 is a poor-prognostic factor, with median survival of 2.3 months (Table 26-1). Important prognostic factors also vary depending on tumor type. KPS, number of brain metastases, extracranial metastasis, and hemoglobin are important prognostic factors for renal cell carcinoma. The updated Disease-Specific Graded Prognostic Assessment (DS-GPA) which incorporated gene and molecular alteration data with clinical factors identified KPS, age, presence of extracranial metastases, number of brain metastases, and the presence of *EGFR* or *ALK* gene alterations for lung cancer and *BRAF* status for melanoma as significant prognostic factors, whereas in breast cancer, the hormonal status (estrogen receptor and progesterone receptor), human epidermal growth factors receptor (EGFR) 2 status, KPS, and age are important factors, but not the number of brain metastases or status of systemic disease.[4,5]

TREATMENT

Management includes supportive care for palliation of symptoms and definitive treatment directed toward the metastases, aiming to prolong survival while preserving quality of life. Most patients die from their systemic disease rather than from their metastases.

TABLE 26-1 ■ Recursive Partitioning Analysis (RPA) Categorization of Patients into Three Prognostic Classes

RPA Class	Factors	Median Survival
1	Age <65 years old KPS ≥ 70 Controlled primary tumor No extracranial metastases	7.1 months
2	All patients not in class 1 or 3	4.2 months
3	KPS <70	2.3 months

KPS, Karnofsky performance status.
Further details are provided by Gaspar LE, Scott C, Murray K, et al: Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys 47:1001, 2000.

Supportive Treatment

Dexamethasone is the corticosteroid of choice in controlling vasogenic edema, as it has a long half-life, the best CNS penetration, the fewest mineralocorticoid side effects, and is the least protein bound. The recommended starting dose is 4 to 8 mg daily for symptomatic patients, and this can be increased to 16 to 32 mg daily for patients presenting with acute signs of increased ICP or with severe symptoms. Its therapeutic effects are usually evident within 24 to 72 hours in up to 75 percent of patients. Once clinical benefit occurs, dexamethasone should be titrated down to the lowest possible dose that provides relief of symptoms, in order to minimize adverse effects. Prophylactic treatment for peptic ulcers is generally not recommended, except for patients with a history of previous ulcer, those taking concurrent nonsteroidal anti-inflammatory drugs, or the elderly. Among patients with brain metastases, 20 percent experience seizures, and antiepileptic drugs (AEDs) should be given when they occur. Older AEDs such as phenytoin, phenobarbital, and carbamazepine induce cytochrome P-450 hepatic enzymes, which potentially can accelerate the metabolism of many chemotherapeutic agents. Because of these drug interactions, nonenzyme-inducing AEDs such as levetiracetam are preferable. Evidence has failed to show benefit of prophylactic AEDs in decreasing the incidence of new-onset seizures, and therefore prophylaxis is not recommended. The benefit for prophylactic AEDs in the perioperative period has not been proven; when AEDs are utilized in this manner, they should be discontinued 1 to 2 weeks postoperatively.

Surgery

Resection of brain metastases is performed to achieve local disease control, provide a histologic diagnosis, promote decompression from elevated ICP, and allow tapering of corticosteroids. Three randomized controlled trials have examined the benefit of surgery combined with whole-brain radiation therapy (WBRT) compared to WBRT alone in patients with a solitary brain metastasis; a fourth randomized trial compared both treatments to surgery alone. These studies demonstrated significant benefits in local disease control and prolongation of functional independence from combination treatment compared to resection or radiotherapy alone, when given to patients with a single metastasis who were 60 years old or less and had controlled systemic disease and good KPS (Table 26-2). For patients with more than one metastasis, surgery is generally limited to removal of the dominant, life-threatening lesion, and to obtain a histologic diagnosis.

Whole-Brain Radiotherapy

Treatment with WBRT targets both gross and microscopic metastases. Significant reduction of local and remote intracranial recurrence has been demonstrated in patients with solitary and oligometastases who received WBRT following surgical resection or stereotactic radiosurgery; however, overall survival and preservation of functional independence did not differ between those treated with or without adjuvant WBRT. An individual patient data meta-analysis of three randomized trials assessing stereotactic radiosurgery with or without WBRT demonstrated a survival advantage for stereotactic radiosurgery alone in patients with one to four brain metastases, KPS of 70 or higher, and age of 50 or younger. Furthermore, in this cohort, no apparent increased risk of new brain metastases was observed, supporting stereotactic radiosurgery alone in patients with up to four brain metastases in this age group. In older patients (>50 years old), WBRT decreased the risk of new brain metastases, but did not affect survival. A phase III trial randomizing patients with one to three brain metastases to stereotactic radiosurgery alone or followed by WBRT demonstrated a more frequent neurocognitive decline in patients who received WBRT after stereotactic radiosurgery without significant difference in survival.[6] For patients with multiple metastases not amenable to surgery or stereotactic radiosurgery, or patients with poor-prognostic factors and limited life expectancy, WBRT is used for palliation of symptoms, prolonging overall survival for up to 3 to 6 months. A phase III randomized trial (QUARTZ) demonstrated that optimal supportive care (OSC) is as effective as OSC with WBRT in patients with nonsmall cell lung cancer with brain metastases unsuitable for surgery or stereotactic radiosurgery. Because of the lack of significant benefit in overall survival and reported neurocognitive toxicity, it is recommended to withhold WBRT after local control with either surgery or stereotactic radiosurgery. The addition of memantine and hippocampal avoidance with WBRT may reduce the risk of neurocognitive decline without a significant difference in intracranial progression-free survival and overall survival.[4,5]

Stereotactic Radiosurgery

Stereotactic radiosurgery is focused radiotherapy in which high-dose, single-fraction irradiation is directed at metastases while sparing the surrounding normal brain tissues from radiation exposure. It can be delivered by linear accelerator or gamma knife. It is beneficial in treating lesions less than 3 cm in size that are located in the eloquent areas, in the deep structures of the brain, or both, when these are not amenable to surgery. Hypofractionated radiosurgery (2 to 5 fractions of smaller doses) is used for larger metastases to decrease the risk of radionecrosis. The risk of radiation-induced neurocognitive dysfunction is markedly less than with WBRT. Retrospective studies comparing surgery and stereotactic radiosurgery report similar outcome. Therefore, the choice between surgery and stereotactic

TABLE 26-2 ■ Randomized Controlled Trials of Patients with Single Brain Metastasis Treated With Surgery, Radiotherapy, or Both

	Median Survival			Duration of Functional Independence		
Population Studies	**Test Group**	**Standard**	**Result**	**Test Group**	**Standard**	**Result**
Surgery + WBRT vs. WBRT[*] $N = 48$	40 weeks	15 weeks	S	38 weeks	8 weeks	S
Surgery + WBRT vs. WBRT[¶] $N = 63$	12 months	7 months	S	9 months	4 months	S
Surgery + WBRT vs. WBRT[¥] $N = 84$	5.6 months	6.3 months	NS	—	—	—
Surgery + WBRT vs. Surgery[§] $N = 95$	48 weeks	43 weeks	NS	37 weeks	35 weeks	NS

WBRT, whole-brain radiotherapy; S, significant; NS, not significant.

Data from [*] Patchell RA, Tibbs PA, Walsh JW, et al: A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322:494, 1990; [¶] Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al: Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Ann Neurol 33:583, 1993; [¥] Mintz AH, Kestle J, Rathbone MP, et al: A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. Cancer 78:1470, 1996; [§] Patchell RA, Tibbs PA, Regine WF, et al: Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 280:1485, 1998.

radiosurgery for local control depends on the number, location, and size of brain metastases, neurologic symptoms, and patient and physician preferences.[4,5]

For patients with unresectable solitary or oligometastases with good prognostic factors (RPA class I), stereotactic radiosurgery following WBRT confers better local control of lesions and stabilization or improvement of performance status compared to WBRT alone, but survival advantage has been demonstrated only in patients with a single metastasis. The addition of stereotactic radiosurgery to WBRT seems in fact to confer survival benefit for patients with a good prognosis regardless of whether they have one, two, or three brain metastases; however, the survival benefit does not extend to patients with a poor prognosis. Randomized controlled trials comparing stereotactic radiosurgery alone or followed by WBRT showed improved local and remote intracranial control with combined treatment, without significant difference in overall survival and performance status. Based on these randomized trials, close monitoring without WBRT following stereotactic radiosurgery is recommended for patients with one to four brain metastases and good performance status.[4,5]

Postoperative stereotactic radiosurgery is another approach to decrease the risk of local recurrence while avoiding the neurocognitive toxicity from WBRT. A phase III randomized trial concluded that stereotactic radiosurgery to the surgical cavity results in improved cognitive outcome, better preservation of quality of life and functional independence compared to postsurgery WBRT, without significant difference in overall survival.[7] Stereotactic radiosurgery should be considered one of the standards of care as a less toxic alternative to WBRT after resection of a brain metastasis.[4,5,7]

Chemotherapy

Chemotherapy is recommended as first-line treatment for chemosensitive brain metastases such as germ cell tumors and non-Hodgkin lymphoma. Response rates to cytotoxic chemotherapy are high in small cell lung cancer (30 to 80%), intermediate rates in breast cancer (30 to 50%) and nonsmall cell lung cancer (10 to 30%), and low rates in melanoma (10 to 15%); responses in the brain do not always parallel those of systemic disease. Treatment response is higher for chemotherapy-naïve tumors, but as most of these patients have already failed previous chemotherapy, radiotherapy is a more effective option in the treatment of brain metastases. Various chemotherapeutic agents in combination with two or three other agents and radiation therapy have been used (Table 26-3).[4,5]

Targeted Therapies

Molecular targeted therapies have shown promising roles in the treatment of brain metastases, including gefitinib, erlotinib, afitinib and osimertinib [epidermal growth factor receptor (EGFR) inhibitors] and crizotinib (ALK and ROS1 inhibitor) for nonsmall cell lung cancer; lapatinib (EGFR and HER2 inhibitors) for HER2-positive breast cancer; and dabrafenib and vemurafenib (BRAF inhibitor) and trametinib (MEK inhibitor) for melanoma (Table 26-3).[4,5]

Immunotherapy

Immunotherapy has shown promising results in treating brain metastases. Emerging data suggest that immune checkpoint inhibitors (ICI) can stimulate T cells peripherally, resulting in antitumor effects in the central nervous system. ICI blocking programmed cell death protein 1 (PD-1) and its ligand (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have shown efficacy in brain metastases (Table 26-3). Pembrolizumab (anti-PD1) monotherapy has shown intracranial response rates of 20 to 30 percent in patients with melanoma and nonsmall cell lung carcinoma; while combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) has demonstrated an intracranial response in 55 percent of patients with brain metastases from melanoma. Radiation therapy with immunotherapy augments antitumor immune responses at a local site as well as at distant metastatic site, known as the abscopal phenomenon.[4,5]

Prophylactic Cranial Irradiation

In malignancies with a high predilection to metastasize to the brain such as small cell lung cancer (SCLC), prophylactic cranial irradiation (PCI) may be used. Patients with limited-stage SCLC who achieve complete response to chemotherapy have a decreased incidence of brain metastases (relative risk 0.46; 95% CI 0.38 to 0.57) and absolute decrease in 3-year cumulative incidence of brain metastases (33% vs. 59%) with PCI.[8] However, while PCI can decrease the incidence of symptomatic brain metastases in extensive-stage SCLC, the impact of PCI on overall survival is uncertain due to differences in the results between

TABLE 26-3 ■ Evolving Systemic Treatment Options for Brain Metastases From Three Common Malignancies

Malignancies	Agents
	Cytotoxic Chemotherapies
NSCLC	Cisplatin or carboplatin, pemetrexed, etoposide, vinorelbine, temozolomide
Breast cancer	Cyclophosphamide, 5-FU, methotrexate, vincristine, cisplatin, etoposide, capecitabine, high-dose methotrexate
Melanoma	Fotemustine, temozolomide
	Targeted therapies
NSCLC	First-generation EGFR-TKI (gefetinib, erlotinib), second-generation EGFR-TKI (afatinib), third-generation EGFR-TKI (osimertinib), first-generation ALK inhibitor (crizotinib), second-generation ALK inhibitor (ceritinib, alectinib), third-generation ALK inhibitors (brigatinib, lorlatinib)
Breast cancer (HER2-positive)	HER-2 inhibitors (trastuzumab, pertuzumab, neratinib), ADC trastuzumab-emtansine (TDM-1), dual EGFR and HER2-TKI (lapatinib), CDK 4/6 inhibitor (abemaciclib)
Melanoma	BRAF V600E inhibitors (dabrafenib, vemurafenib), MEK inhibitor (trametinib), cKIT inhibitors (imatinib, dasatinib)
	Immunotherapies
NSCLC	Anti-PD1 (nivolumab, pembrolizumab)
Melanoma	Anti-PD1(nivolumab, pembrolizumab), Anti-CTLA4 (ipilimumab)

NSCLC, Nonsmall cell lung cancer; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase; CDK, cyclin-dependent kinase; ADC, antibody–drug conjugate; PD1, programmed death receptor 1; CTLA4, cytotoxic T-lymphocyte-associated protein 4; MEK, mitogen-activated protein kinase.

two phase III randomized trials. Thus, individualized discussion is recommended in patients with extensive-stage SCLC due to the risk of radiation-induced side effects and insufficient evidence on survival benefit of PCI. This prophylactic strategy has not shown the same degree of benefit in NSCLC.

Skull Base

DEFINITION AND EPIDEMIOLOGY

The base of the skull forms the floor of the cranial cavity and is composed of the ethmoid, sphenoid, occipital, paired frontal, and paired parietal bones. Metastases to the skull base may involve the cranial nerves and blood vessels that pass through foramina in these bones. Skull-base metastases occur in 4 percent of cancer patients, frequently late in the course of the disease. The most common responsible primary malignancies are prostate (38.5%), breast (20.5%), lymphoma (8%), and lung (6%).[9]

PATHOPHYSIOLOGY

The skull base may become involved directly from hematogenous spread of malignant cells or by retrograde seeding through the Batson plexus, a common route in prostate carcinoma. Osseous metastases may entrap and compress the nearby cranial nerves and vessels, producing neurologic signs and symptoms. Direct extension from head and neck malignancies may also involve the skull base.[9]

CLINICAL FEATURES

Skull-base metastases produce symptoms when they enlarge and compress surrounding structures, causing pain and neurologic deficits. The development of cranial neuropathies or craniofacial pain in patients with malignancy should raise the suspicion of skull-base metastases. Cranial neuropathies are the presenting symptom in 28 percent of patients with such metastases. The extraocular motor nerves are most commonly involved, followed by the trigeminal and hypoglossal nerves. The anatomic location involved can lead to specific clinical syndromes, including orbital syndrome in 12.5 percent, parasellar and sellar syndromes in 29 percent, middle fossa syndromes in 6 percent, jugular foramen syndromes in 3.5 percent, and occipital condyle syndrome in 16 percent of patients (Table 26-4).[9]

DIAGNOSTIC STUDIES

Advances in MRI techniques have greatly improved the identification and evaluation of the extent of skull-base metastases, including bone marrow invasion, perineural spread, and cranial nerve, leptomeningeal, and brain parenchymal involvement (Fig. 26-3). Radionuclide bone scanning can detect skull-base metastases in 30 to 50 percent of these patients, but it has a relatively poor sensitivity in detecting purely lytic lesions. CT using bone windowing is the best means of detecting lytic bone destruction. Dual-isotope single-photon emission computed tomography (SPECT) may show increased uptake in the skull base. CSF examination and biopsy, including endoscopic and minimally invasive techniques, are sometimes indicated to establish the diagnosis of skull-base metastases.

Differential Diagnosis

Primary skull tumors, such as osteoma and chondrosarcoma, and benign tumor-like lesions including fibrous dysplasia may appear radiographically similar to skull-base metastases. Patients with metastases are generally older, with a median age of 70 years, have shorter duration of symptoms (median of 2 months), and present less frequently with neurologic deficits than patients with these other lesions.[9]

Treatment

Radiation therapy is the standard treatment, providing pain relief, improvement of cranial nerve dysfunction and local control. The beneficial effects parallel the timing of irradiation—87 percent of patients who receive radiation within 1 month of symptom onset show clinical improvement compared with 25 percent of patients treated after 3 months. Stereotactic radiosurgery provides clinical improvement in 62 percent and tumor control in 67 to 95 percent of patients, and can be used as an initial treatment, especially for lesions near neural structures and for previously irradiated tumors. For chemosensitive tumors such as breast and prostate carcinomas, chemotherapy and hormonal therapy in combination with radiation therapy offer survival benefits. Surgery may be considered for radioresistant tumors such as melanoma, renal cell carcinomas, and sarcomas, as well as in patients with rapid neurologic decline, such as visual loss, with the goal of preserving neurologic status and symptom relief.[9]

Prognosis

Skull-base metastases are typically seen in disseminated malignancies, and the overall median survival is 31 months. Patients with metastases from breast carcinoma have the best survival (60 months); prostate carcinoma and lymphoma, intermediate survival; and lung and colon carcinomas the worst survival (2.5 and 2.1 months, respectively).[9]

Intracranial Dura

Definition and Epidemiology

Carcinomatous infiltration of the dura and epidural space is found at autopsy in 9 to 14 percent of

TABLE 26-4 ■ Skull-Base Syndromes, Associated Cranial Neuropathies, Accompanying Findings, and Most Common Primary Malignancies

Skull-Base Syndromes	Cranial Neuropathies	Associated Findings	Common Primary Malignancies
Orbital syndrome	CN II, III, IV, VI, and V-1	Supraorbital frontal headache, pain, diplopia, proptosis, periorbital swelling, decreased vision	Prostate cancer Lymphoma Breast cancer
Parasellar/cavernous sinus syndrome	CN III, IV, VI, V-1, and V-2	Supraorbital frontal headache, no proptosis, vision may be affected late in the course	Lymphoma
Middle fossa/Gasserian ganglion syndrome	CN V-2 and V-3 sensory and motor roots; CN III, IV, VI, and VII (less common)	Lightning-like facial pain, sparing the forehead; headache is uncommon	Breast cancer Lung cancer
Jugular foramen syndrome	CN IX, X and XI (Vernet syndrome) plus CN XII (Collet–Sicard syndrome)	Unilateral occipital and postauricular pain; dysphagia; hoarseness; Horner syndrome	Breast cancer Melanoma Ewing sarcoma Prostate cancer
Occipital condyle	CN XII	Occipital pain, stiff neck	Breast cancer Prostate cancer
Numb chin syndrome	Mental nerve	Unilateral anesthesia of chin and lower lip	Breast cancer Lymphoma Melanoma Lung cancer Prostate cancer

Derived from Harrison RA, Nam JY, Weathers SP, et al: Intracranial dural, calvarial, and skull base metastases. Handb Clin Neurol 149:205, 2018.

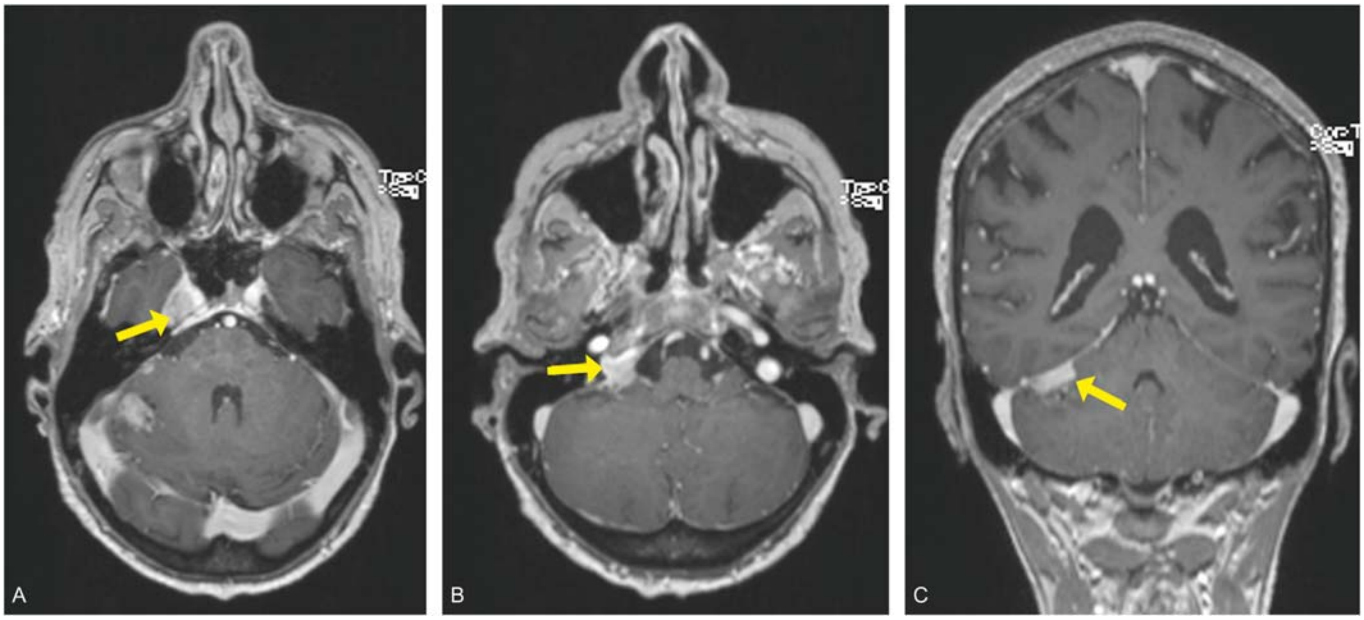

FIGURE 26-3 ■ Skull-base metastases. A 73-year-old patient with history of nonsmall cell lung carcinoma presented with right cavernous sinus syndrome. MRI demonstrates multiple avidly enhancing lesions within *A*, the right Meckel cave and *B*, the right jugular foramen. Dural-based metastases also are seen *C*, along the inferior surface of the right tentorium.

patients with primary malignancies. Common primary tumors include breast, prostate, and lung carcinomas. They are more common in women; the mean age at diagnosis is 59 years.[9]

Pathophysiology

A majority of patients develop intracranial dural metastases by direct extension from skull metastases, whereas hematogenous spread accounts for 33 to 43 percent. Nontraumatic subdural hematoma occurs in 15 to 40 percent of patients, presumably due to rupture of fragile tumor vessels and to mechanical obstruction of external dural vessels leading to dilation and rupture of dural capillaries. Chronic subdural hematoma alters the barrier properties of the dura, promoting tumor infiltration.[9]

Clinical Features

Dural metastases produce symptoms through traction of the dura, invasion of venous sinuses, elevation of ICP, and compression of the underlying brain parenchyma, cavernous sinus, and surrounding neural structures. Common presentations include headache, cranial neuropathies, visual changes, altered mentation, and seizures. The presence of new or localized headache in these patients is suggestive of subdural hematoma and should prompt imaging. Between 11 and 50 percent of patients are asymptomatic, diagnosed incidentally on imaging or at autopsy.[9]

Diagnostic Studies and Differential Diagnosis

Gadolinium-enhanced MRI is the imaging study of choice for identification of dural metastases. These lesions typically enhance homogeneously and may be single or multiple. They may appear as localized or diffuse thickening or nodular enhancement of the dura (Fig. 26-4). CT scan can detect bony involvement. The main differential diagnosis is meningioma, which also presents as an extra-axial, well-circumscribed, hyperdense, contrast-enhancing lesion with a dural tail and hyperostosis of overlying bone. High-lipid signal in MR spectroscopy, a low relative cerebral blood volume in dynamic contrast (perfusion) MRI, increased FDG-PET uptake, and accumulation of tracer in octreotide brain scintigraphy all favor metastasis over meningioma. Pachymeningeal metastases demonstrate dural enhancement localized under the inner table of the skull and do not follow the contour of the gyri in contrast to leptomeningeal involvement.[9]

Treatment

Surgical resection improves overall survival and should be considered as initial treatment for patients with controlled systemic disease and a single, symptomatic,

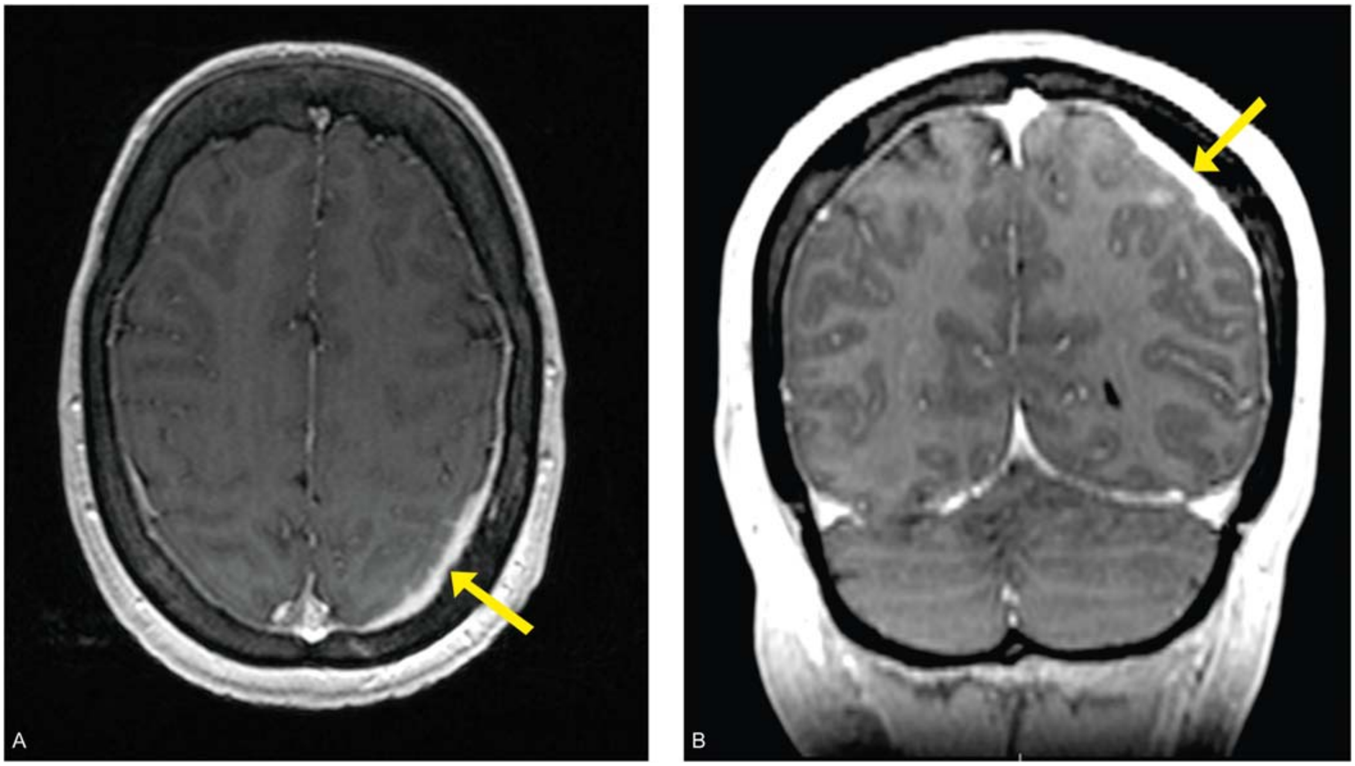

FIGURE 26-4 ■ Dural metastasis from breast cancer. Axial, *A*, and coronal, *B*, T1-weighted, contrast-enhanced brain MR images demonstrating dural thickening along the left parietal convexity.

resectable intracranial dural metastasis. Stereotactic radiosurgery also improves local control. Systemic chemotherapy prolongs progression-free survival, perhaps because dural metastases are outside the blood–brain barrier. For patients who are not candidates for surgery, have poor-performance status, and short-life expectancy, focal or whole-brain radiation can be considered.

PROGNOSIS

The overall median survival is 6 to 9.5 months and progression-free survival is 3.7 months with dural metastases. Patients with primary hematologic malignancies or breast and prostate carcinomas have relatively favorable courses compared to those with other primary cancers. Poor-performance status and lung carcinoma are adverse prognostic factors, while treatment with resection and chemotherapy is associated with improved overall and progression-free survival.[9]

Spine and Spinal Cord

EPIDEMIOLOGY

Bone is the most common site of metastases, and the axial skeleton is the most frequent site affected. Autopsy series reveal spinal metastasis in more than 70 percent of patients with disseminated cancer. The incidence is greatest for breast (73%) and prostate (68%) cancers, followed by thyroid (42%), kidney (35%), and lung (36%) cancers. Spinal metastases are 20 times more common than primary spinal tumors.[10]

CLASSIFICATION BY ANATOMIC LOCATION

Spinal tumors are classified according to anatomic location (Table 26-5). Extradural metastases account for more than 94 percent of secondary spinal tumors. Most arise from the vertebral bodies and extend to the spinal canal, eventually compressing the spinal cord or cauda equina. Intradural extramedullary metastases are rare and usually represent tertiary spread via CSF from cerebral metastases to the cauda equina, termed "drop metastasis." Intramedullary metastases account for about 3.5 percent of spinal metastases and are increasing in frequency, likely due to improvement in detection.[10]

EPIDURAL SPINAL CORD COMPRESSION

Epidemiology

The annual incidence of hospitalization related to epidural spinal cord compression among patients

TABLE 26-5 ■ Anatomic Categories of Spinal Cord Tumors

Anatomic Locations	Tumors
Extradural	Metastases Chordomas Sarcomas Lymphomas Plasmacytomas and multiple myeloma
Intradural, extramedullary	Meningioma Nerve sheath tumors
Intramedullary	Ependymomas Astrocytomas Metastases

with cancer is 3.4 percent. The most common primary sources are lung, breast, and prostate cancer, and multiple myeloma. The thoracic spine is most commonly involved (70%), followed by the lumbar (20%) and cervical (10%) spine; this distribution reflects the number and volume of vertebral bodies in each spinal segment. Multiple noncontiguous lesions are common, occurring in 10 to 40 percent of cases.[10]

Pathophysiology

Epidural spinal cord compression occurs when tumor invades the epidural space and compresses the thecal sac. This results from several mechanisms. Hematogenous spread is the most common route, occurring in 85 percent of cases. The Batson venous plexus drains the vertebrae and skull and forms anastomoses with veins draining the thoracic, abdominal, and pelvic organs and breast. This valveless venous system serves as a pathway to transmit metastatic cells to the spinal column. Tumor cells may also seed via the arterial circulation to the vertebral bodies, which have a relatively large blood flow. Metastatic cells cause vertebral bone destruction, mass expansion within the vertebral body, and eventual outgrowth into the epidural space. Less commonly, tumor cells from the paraspinal region reach the epidural space directly through the intervertebral foramen, particularly in patients with lymphoma and neuroblastoma. Direct hematogenous metastasis to the epidural space is rare.

Direct mechanical injury to the axons and myelin, along with secondary vascular compromise of the epidural venous plexus and spinal arteries, results in spinal cord edema, infarction, and subsequent dysfunction. Tumor production of VEGF is also associated with spinal cord hypoxia. In addition, tumor invasion of the bony spine can harm the spinal cord by destabilization of the spinal column.[10]

Clinical Features

Back pain is the most common presenting symptom, affecting more than 95 percent of patients with epidural spinal cord compression. The pain is initially localized over the involved vertebral bodies and is attributable to stretching of the periosteum and other adjacent pain-sensitive structures. It is typically chronic, with a median duration of 2 months, and increases in severity over time. It is frequently worse with the Valsalva maneuver and recumbency as a result of distention of the venous plexus. When nerve roots are involved, patients may complain of radicular pain or a tight band around the chest and abdomen. Acute pain raises the suspicion of pathologic compression fracture. Pain on movement suggests mechanical instability. The Spine Instability Neoplastic Score, a classification system based on six clinical and radiographic criteria, aids clinicians in predicting spine stability and assists in treatment decision-making.[11] Motor deficits are the second most common symptom (60 to 85%) followed by sensory symptoms (60%). The weakness may be upper motor neuron in type from compression of the spinal cord when the lesion is above the L1−2 vertebral bodies, or lower motor neuron in type from compression of the cauda equina when the lesion is below this level. More than half of patients with epidural spinal cord compression are nonambulatory upon diagnosis. Spinal cord compression produces a sensory level at or above the level of epidural involvement, and nerve root compression results in a dermatomal pattern of sensory deficits. Patients with compression of the posterior columns in the cervical and upper thoracic segments of the spinal cord may experience the Lhermitte phenomenon. Autonomic symptoms, including bowel and bladder dysfunction, sexual disturbance, and orthostatic hypotension, tend to occur late in the course of epidural spinal cord compression.[10,12]

Diagnostic Studies

Epidural spinal cord compression is a neuro-oncologic emergency as neurologic deficits may progress rapidly. MRI is optimal for detecting the lesion, with an overall accuracy of at least 95 percent. Because

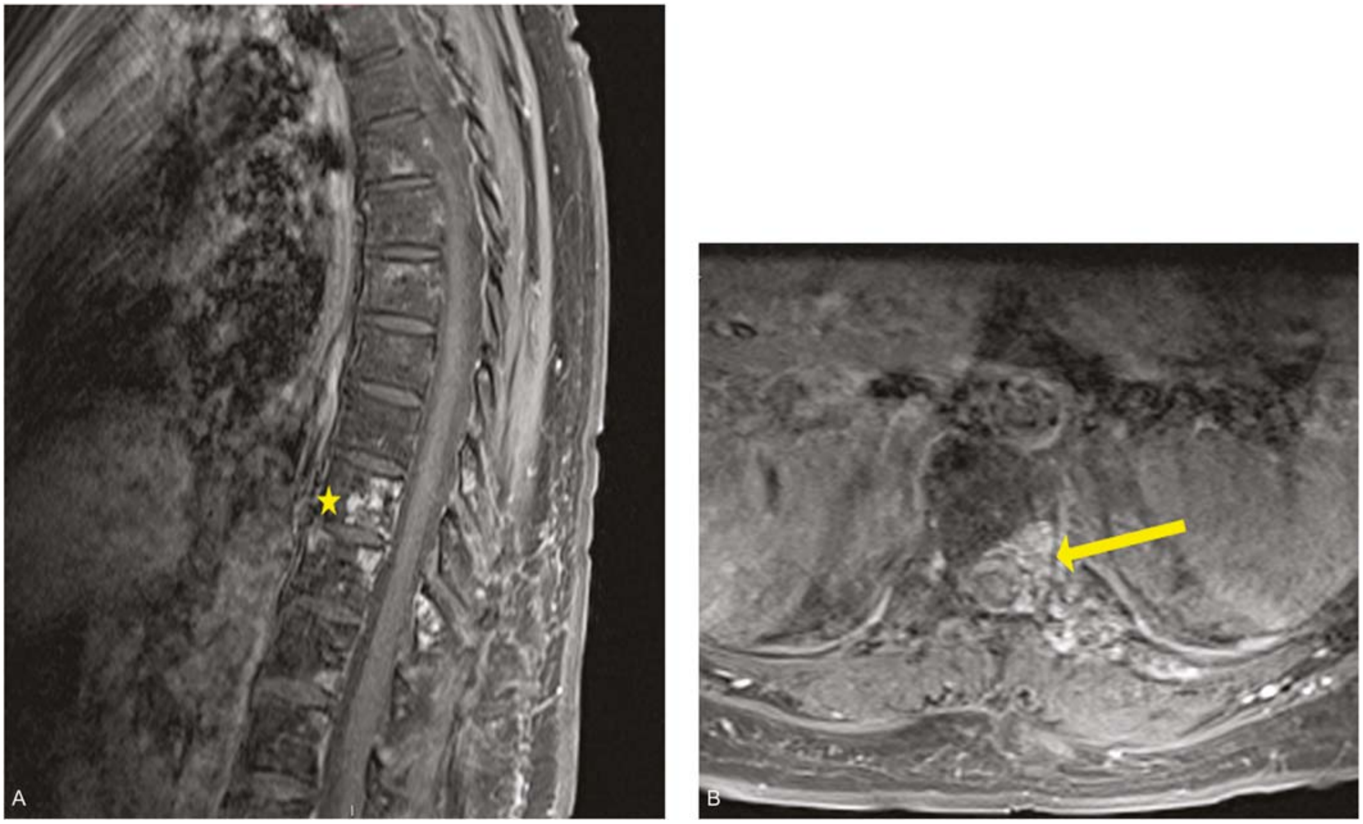

FIGURE 26-5 ■ Epidural spinal cord compression secondary to metastatic breast cancer. Postcontrast MRI demonstrates, *A*, numerous metastatic lesions involving nearly all the thoracic vertebral bodies, with greatest involvement at the T9 vertebral body (*star*). There is mild neuroforaminal encroachment by the tumor at the left T9-10 level, *B*.

multiple lesions are common, the entire spine should be imaged. Vertebral metastases appear hypointense on T1-weighted MRI sequences, hyperintense on T2-weighted sequences, and show postgadolinium enhancement (Fig. 26-5). A scale has been developed to describe the degree of spinal cord compression based on axial T2-weighted MR images and this may guide treatment decisions (Table 26-6). Increased T2 signal within the spinal cord represents venous congestion or ischemia. For patients in whom MRI is contraindicated, CT myelography is an acceptable alternative. Plain radiography, bone scans, and spinal CT do not adequately depict the tumor, spinal cord, and paraspinal region. Around 80 percent of patients with epidural spinal cord compression have a known systemic malignancy, and immediate treatment should be initiated once the diagnosis is made. For patients without prior history of cancer, biopsy of the paraspinal or vertebral lesion to make a tissue diagnosis is warranted.[10,12]

TABLE 26-6 ■ **Epidural Spinal Cord Compression (ESCC) Score**

Grades		Description
Low-grade	0	Tumor confined to the bone only
	1	Tumor with epidural extension without contact with the spinal cord or just spinal cord abutment without displacement
	1a	Epidural impingement, without thecal sac compression
	1b	Epidural tumor with thecal sac compression, without spinal cord abutment
	1c	Epidural tumor with thecal sac compression, with spinal cord abutment, without cord compression
High-grade	2	Tumor compresses the spinal cord, with CSF visible around the cord
	3	Tumor compresses the spinal cord, with no CSF visible around the cord

Derived from Bilsky MH, Laufer I, Fourney DR, et al: Reliability analysis of the epidural spinal cord compression scale. J Neurosurg Spine 13:324, 2010.

Treatment

The goals of treatment are palliative, including pain relief and preservation or recovery of neurologic function, maintenance of spinal stability, durable local tumor control, and improved quality of life. A decision framework, NOMS (neurologic, oncologic, mechanical instability, and systemic disease), has been developed to facilitate treatment decision-making in patients with metastatic spine tumors.[13] The neurologic assessment evaluates the presence of myelopathy, functional radiculopathy, and degree of epidural spinal cord compression (high-grade vs. low-grade compression). The oncologic consideration is based on the expected tumoral response and durability of response to available treatments, including surgery, radiation therapy, and systemic treatment. Mechanical instability is a separate consideration, because symptomatic pathologic fractures do not respond to radiation alone and typically require stabilization. The fourth consideration is the extent of systemic disease and presence of medical co-morbidities that affect the risk—benefit ratio of a proposed treatment and expected overall survival based on extent of disease and tumor histology.[12]

Corticosteroids, typically dexamethasone, are recommended for patients with neurologic deficits. They may temporarily stabilize neurologic dysfunction by reducing tumor and spinal cord edema, alleviate pain through antiprostaglandin effects, and have a direct cytotoxic effect on certain malignancies such as lymphoma and multiple myeloma. Patients with minimal or nonprogressive weakness may receive moderate dexamethasone doses (e.g., 8 to 10 mg loading dose, followed by 16 mg/day in divided doses). Some treat patients with rapidly progressive motor symptoms with higher doses, such as with a 100 mg loading dose followed by up to 96 mg/day. When these high doses are used, rapid taper is important to minimize the risk of complications such as steroid myopathies and peptic ulcers.[10]

The objectives of surgery include obtaining a histologic diagnosis, local tumor control, pain relief, and spinal cord decompression and removal of epidural disease to allow spinal stereotactic radiosurgery and stereotactic body radiotherapy (SBRT). Other aims are to restore neurologic status, reestablish spine stability, and correct deformity. Compared to patients treated with radiotherapy alone, patients undergoing timely surgery followed by radiation therapy are more likely to recover or maintain ambulation, achieve better pain control, have preservation of continence, and experience longer median survival. Surgical stabilization followed by decompression in patients with radioresistant tumors with high-grade compression is strongly recommended. The advent of spinal stereotactic radiosurgery as postoperative adjuvant treatment has changed the goals of surgery. The surgical goal is now to create a target for safe delivery of spinal stereotactic radiosurgery rather than maximal debulking followed by external beam radiation therapy. Separation surgery focuses on reconstitution of spinal fluid space to create a 2-mm margin between the tumor and spinal cord, but without resection of the vertebral body or paraspinal tumor, leaving the bulk of the tumor to be treated by radiation. Separation surgery followed by spinal stereotactic radiosurgery is safe and effective in durable local tumor control regardless of tumor histology-specific radiosensitivity.[12]

Conventional external beam radiation therapy improves back pain (in 60% of patients), ambulation (70%), and continence (90%). Important predictors of response to radiotherapy include performance status at the start of treatment, tumor radiosensitivity, and rapidity of onset of neurologic deficits. Radiosensitive tumors such as myeloma, lymphoma, seminoma, small cell lung cancer, prostate cancer, and breast carcinomas respond better than generally radioresistant metastases such as melanoma, osteosarcoma, gastrointestinal cancers, and renal cell carcinoma. For patients with a poor prognosis, two fractions of 8 Gy given 1 week apart are recommended, while those with a good prognosis are given higher total doses with more fractions. The most common dose and fractionation schedule being utilized in the United States is 30 Gy divided into 10 fractions.[10,12]

The effectiveness of conventional external beam radiation therapy to spinal metastases is limited due to poor-radiation tolerance of the spinal cord. For this reason, stereotactic radiosurgery has been utilized increasingly to treat spinal metastases, allowing safe delivery of high-dose radiation to metastases within or adjacent to the vertebral bodies and spinal cord, while minimizing toxicity to the surrounding structures. High-dose single stereotactic radiosurgery (16 to 24 Gy) or hypofractionated (24 to 30 Gy in two to three fractions) stereotactic body radiotherapy offers a significantly higher biologic effective dose and more precise dose delivery with shorter treatment schedule compared to external beam radiation therapy. The higher dose of stereotactic radiosurgery increases the percentage of DNA damage and obviates the histologic dependence that exists in conventional radiation therapy, with 12-month local control rates of over 85 percent, including classically radioresistant tumors. Because stereotactic radiosurgery has a steep fall-off gradient of target dose with negligible skin effects, it can be given soon after surgery without concern for wound complications. The complications of spinal stereotactic radiosurgery are generally mild and self-limited.[12]

Chemotherapy has a limited role in patients with epidural spinal cord compression because of the need to decompress the spinal cord urgently in order to preserve neurologic functions. In patients with chemosensitive tumors such as lymphoma and seminoma who have minimal or no neurologic deficits, chemotherapy may be considered. The combination of spinal stereotactic radiosurgery with immunotherapy demonstrates promising results by inducing an abscopal effect, leading to improvement of systemic disease control.[10]

Prognosis

The median survival following diagnosis of metastatic epidural spinal cord compression is historically reported at 3 to 6 months. However, with improvements in treatment, many patients survive for several years after treatment. The strongest factors affecting survival include the degree of neurologic deficit at the time of diagnosis and the primary tumor type. Patients with hematologic malignancies, breast cancer, and prostate cancer have longer survival, while those with carcinoma of the lung have the shortest. Nonambulatory patients do poorly, and those with bladder and bowel dysfunction have the worst prognosis.[10,12]

INTRAMEDULLARY SPINAL CORD METASTASES

Epidemiology and Pathophysiology

Intramedullary spinal cord metastases are rare, usually encountered in the setting of extensive metastatic disease. These metastases are typically solitary and can occur in any segment of the spinal cord. The majority of patients have concomitant brain metastases and one-quarter have leptomeningeal carcinomatosis. Almost half of intramedullary spinal cord metastases originate from lung cancer, particularly small cell lung cancer; less common primary neoplasms are melanoma, lymphoma, and breast, colorectal, and renal cell cancer. Tumor cells reach the parenchyma of the spinal cord by hematogenous dissemination, direct extension from leptomeninges, along nerve roots, or through Virchow–Robin spaces.[10]

Clinical Features

Weakness is present in 90 percent of patients at the time of diagnosis. Other common presentations are sensory loss, sphincter dysfunction, back pain, and radicular pain. Neurologic deficits develop much earlier, usually soon after the onset of spinal or radicular pain, than in patients with epidural spinal cord compression. The presence of a Brown-Séquard syndrome or asymmetric myelopathy strongly suggests intramedullary rather than epidural metastases. Intramedullary metastases may be mistaken for radiation myelopathy, but can be differentiated by the slow and relatively painless presentation of the latter.

Diagnostic Studies

MRI with gadolinium enhancement reliably identifies intramedullary metastases, which appear as well-defined lesions with avid contrast enhancement that are hypointense on T1- and hyperintense on T2-weighted sequences; prominent surrounding edema is common (Fig. 26-6). Spinal MRI may also detect concomitant leptomeningeal involvement. Brain MRI should be performed even in the absence of cerebral symptoms, as concurrent brain metastases are common.

Treatment and Prognosis

Fractionated radiotherapy is the main treatment modality for intramedullary metastases. The goals of radiotherapy are to control tumor growth, palliate symptoms, and improve neurologic deficits. With the development of new techniques including MR or CT navigation, cavitron ultrasonic surgical aspiration, and intraoperative electrophysiologic monitoring, surgical excision has been used increasingly in patients with limited systemic disease and radioresistant tumors. In general, patients with intramedullary spinal cord metastases have a limited clinical response to treatment and a very poor prognosis, with a median survival of 4 months.[10]

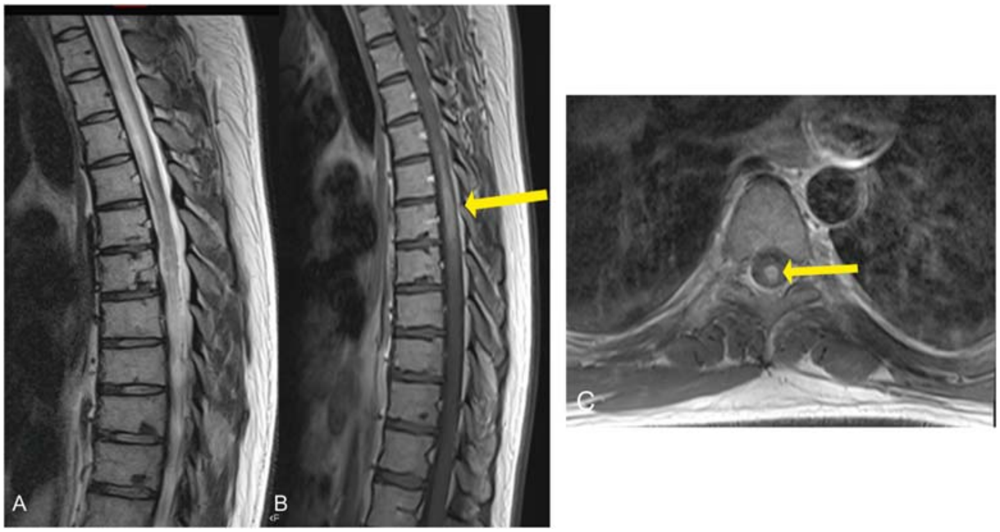

FIGURE 26-6 ■ Intramedullary spinal cord metastases from parotid salivary ductal carcinoma. *A*, Diffuse expansile hyperintense T2 signal within the thoracic cord. *B* and *C*, Enhancing intramedullary lesion, centered at the level of T6.

Leptomeninges

Definition

Leptomeningeal metastasis or neoplastic meningitis refers to the dissemination of cancer cells to the CSF, pia, and arachnoid mater. Depending on the underlying malignancy, this condition may be termed leptomeningeal carcinomatosis, lymphomatous meningitis, or leukemic meningitis.[14]

Epidemiology

Leptomeningeal carcinomatosis is diagnosed in 5 to 10 percent of patients with solid cancers and 5 to 20 percent of those with hematologic malignancies. It also occurs in 1 to 2 percent of patients with primary brain tumors. The most common solid tumor sources are breast (12 to 34%), lung (10 to 26%) carcinomas, and melanoma (17 to 25%), while the most common hematologic tumor sources are acute lymphoblastic leukemia (10%), acute myeloid leukemia (5 to 10%), primary CNS or ocular lymphoma (20%), and non-Hodgkin's lymphoma (20%). The median age of diagnosis is 56 years and median KPS is 70. More than 70 percent of patients with leptomeningeal disease have advanced and uncontrolled systemic disease. Approximately 19 percent of cancer patients with neurologic signs and symptoms have evidence of leptomeningeal metastases on autopsy studies.[14]

Pathophysiology

Leptomeningeal seeding occurs through several mechanisms, including hematogenous spread via Batson plexus or arterial dissemination, direct extension from adjacent structures, and migration from systemic tumors along perineural or perivascular spaces. Once tumor cells reach the leptomeninges, they can spread throughout the CNS via the CSF, resulting in multifocal neuraxis seeding. Tumor infiltration is most prominent in the skull base, the posterior surface of the spinal cord, and cauda equina, producing cranial nerve palsies and radiculopathies. Tumor deposits may result in obstruction of CSF flow, leading to hydrocephalus and sometimes to increased ICP. Blood vessels crossing the subarachnoid space may become occluded, leading to cerebral or spinal infarction.[14]

Clinical Features

Clinical manifestations of leptomeningeal metastases can be classified into three categories: cerebral involvement resulting in headache, altered mental status, nausea, vomiting, gait disturbance, and cerebellar signs; cranial nerve involvement presenting with diplopia, visual loss, hearing changes, and facial weakness; and spinal symptoms including weakness, paresthesias, radicular neck or back pain, and bowel or bladder dysfunction. The majority of patients present with multifocal symptoms.

Diagnostic Studies

Gadolinium-enhanced MRI of the entire neuraxis is warranted to evaluate the extent of CNS disease and plan treatment. Neuroimaging should precede lumbar puncture as intracranial hypotension from lumbar puncture may produce pachymeningeal enhancement that mimics leptomeningeal metastases.

MRI findings that are highly suggestive of leptomeningeal metastases include linear or nodular enhancement of leptomeninges, which is often visible in the cerebral sulci, cerebellar folia, basal cisterns, and cauda equina; enhancement of the subependyma, and cranial or spinal nerves; and hydrocephalus (Fig. 26-7). A high-clinical suspicion of leptomeningeal metastases coupled with consistent MRI findings is sufficient to establish the diagnosis, even in the absence of malignant cells on CSF cytology.[14]

While identifying malignant cells in the CSF is the gold standard for diagnosis, its sensitivity is low. To minimize false-negative studies, the following measures are recommended: withdrawal of at least 10.5 ml of CSF for analysis; immediate processing of the sample; obtaining CSF from a site adjacent to the affected CNS region; and repeated CSF sampling and analysis. The sensitivity of CSF cytology is 71 percent for the first sample, 86 percent after two samples, 90 percent following three samples, and up to 93 percent after more than three samples. Flow cytometry analysis improves this sensitivity for patients with hematologic malignancies. Other CSF parameters suggestive of leptomeningeal metastases are elevated opening pressure, elevated leukocyte count, increased protein content, and decreased glucose level. CSF flow block develops at various levels in 30 to 70 percent of patients with leptomeningeal metastases and can be seen with radionuclide studies. Several organ-specific biomarkers in the CSF such as CA 15-3 in breast cancer and CEA and Cyfra 21.1 in nonsmall cell lung cancer, may assist in diagnosis. Isolation and quantification of circulating tumor cells can detect malignant cells in CSF through the use of immunoflow cytometry technique with fluorescently labeled antibodies. In epithelial tumors, an antibody against epithelial cell adhesion molecule (EpCAM) is used, as this protein is expressed in various epithelial cancers such as breast, lung, and gastrointestinal cancers; high-molecular-weight melanoma-associated antigen/melanoma chondroitin sulfate proteoglycan (HMW-MAA/MCSP) is used for melanoma. Available studies on circulating tumor cells in the CSF of patients with leptomeningeal metastases have a reported sensitivity of 78 to 100 percent, compared to 44 to 67 percent with cytology at first lumbar puncture. The specificity of circulating tumor cells

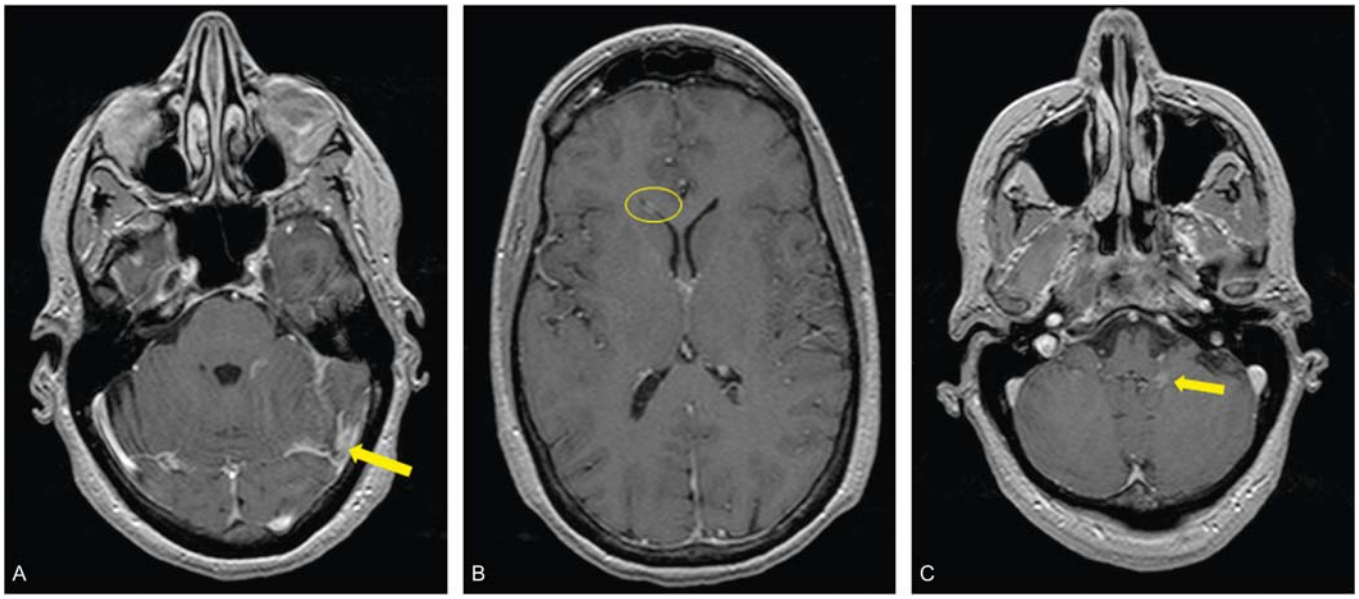

FIGURE 26-7 ▪ Leptomeningeal metastasis from breast carcinoma. Postcontrast MRI demonstrates leptomeningeal enhancement along the left superior cerebellar surface in *A*, the margin of the frontal horn of the right lateral ventricle in *B*, and the left foramen of Luschka in *C*.

ranged between 84 and 100 percent. However, prospective studies with larger samples are required to validate these findings.[14,15]

TREATMENT

Goals of treatment are to improve or stabilize neurologic function, maintain quality of life, and prolong survival. Treatment optimally should be directed toward the entire neuraxis, as tumor cells are disseminated widely throughout the CSF. However, craniospinal radiotherapy is rarely employed because of its significant adverse effects such as gastrointestinal toxicity, mucositis, and bone marrow suppression, and the lack of significant improvement in survival compared to chemotherapy. Involved-field radiotherapy to sites of symptomatic or bulky disease provides palliation of symptoms, treatment of bulky disease, and restoration of CSF flow. Whole-brain radiation therapy and/or placement of a ventriculoperitoneal shunt may be required for patients with communicating hydrocephalus. Patients with breast cancer, leukemia, and lymphoma have a higher likelihood than those with other malignancies of responding to radiotherapy.[14]

Chemotherapy can be given systemically or by the intrathecal route. Systemic chemotherapy can treat both leptomeningeal and systemic disease. Since the blood—brain barrier is intact or only partially disrupted in leptomeningeal disease, agents that are lipid soluble and can be administered safely and achieve a therapeutic level of CSF penetration at higher doses are utilized, such as methotrexate (3 to 8 g/m^2) or cytarabine (3 g/m^2). Other drugs that can cross the blood—brain barrier are capecitabine, thiotepa, and temozolomide. Tumor histology and response to prior drug exposure guide the choice of chemotherapeutic agent.

Intrathecal delivery has several advantages over systemic chemotherapy, including circumvention of the blood—brain barrier and reduction of systemic adverse effects because the drug is delivered directly into the subarachnoid space, and reduced overall dosage. This approach is not appropriate for bulky leptomeningeal diseases as drug concentration is only 1 to 2 percent of the CSF concentration at 1 to 2 mm from the surface. Agents primarily given by the intrathecal route are methotrexate and cytarabine (Ara-C). Randomized trials demonstrated no difference in survival using single-agent methotrexate or thiotepa compared to a combination of methotrexate, thiotepa, and cytarabine in patients with leptomeningeal carcinomatosis from solid tumors. Intrathecal administration of rituximab, an anti-CD20 monoclonal antibody, and trastuzumab, an antihuman epidermal growth factor receptor (HER-2) monoclonal antibody, have been investigated for lymphomatous meningitis and HER-2-positive breast leptomeningeal metastases, respectively, but are not considered standard yet. Intrathecal agents can be delivered via lumbar puncture or intraventricular (Ommaya) reservoir. Repeated lumbar punctures are inconvenient for patients, may result in inadvertent delivery of drugs outside the thecal sac, and produce a more variable drug concentration than intraventricular administration. Although ventricular reservoirs are usually well tolerated, complications such as misplacement, catheter tip occlusion, and infection may occur.[14]

Systemic administration of targeted therapies has shown clinical benefits, such as epidermal growth factors (EGFR) tyrosine kinase inhibitors (erlotinib, gefitinib, and osimertinib) in patients with nonsmall cell lung cancer, anaplastic lymphoma kinase (ALK) inhibitors (crizotinib, ceritinib and alectinib) in ALK fusion-positive nonsmall cell lung cancer patients, trastuzumab in HER2-positive breast cancer, and BRAF inhibitors (dabrafenib and vemurafenib) for melanoma. Prospective trials are needed to validate these findings. Due to limited CNS penetration at standard daily dosing, an intermittent "pulsatile" administration of high-dose tyrosine kinase inhibitors can boost CSF drug concentration. Pulsatile erlotinib is a reasonable alternative in EGFR-positive nonsmall cell lung cancer patients with new or worsening leptomeningeal or brain metastases, without evidence of systemic progression during standard erlotinib dose.[14]

Aggressive supportive treatment should be given to all patients with leptomeningeal metastases including corticosteroids for vasogenic edema and increased ICP, AEDs for seizures, opioid drugs for adequate analgesia, and antidepressants and anxiolytics as needed.

PROGNOSIS

The median survival for untreated leptomeningeal metastases is 4 to 6 weeks, and death often results from progressive neurologic dysfunction. With treatment, median survival is increased to 4 to 8 months. Patients with hematologic tumors have improved survival (median of 4.7 months) compared with solid tumors (median of 2.3 months). Tumor histology and molecular types are also important prognostic factors. The National Comprehensive Cancer Network suggests stratifying patients into either good- or poor-risk groups to guide decision-making regarding treatment. Patients with poor risk are those with low KPS, multiple, serious, or major neurologic deficits, extensive systemic disease with few treatment options, bulky CNS disease, leptomeningeal disease-related encephalopathy, and the presence of CSF block. The goal of treatment for these poor-risk patients is palliation of symptoms. For patients with better risk factors, a more aggressive treatment approach is recommended.

METASTASES TO THE PERIPHERAL NERVOUS SYSTEM

Plexuses

DEFINITION AND EPIDEMIOLOGY

Metastatic plexopathy affects 1 percent of cancer patients and may involve the cervical, brachial, or lumbosacral plexus.[16]

PATHOPHYSIOLOGY

Involvement of the plexus can occur by direct extension from contiguous tumors, from metastases to adjacent soft tissue, bony structures, or lymph nodes, or rarely by direct metastases to the nerves within the plexuses.

ANATOMIC CONSIDERATIONS AND CLINICAL FEATURES

Neurologic manifestations depend on the involved plexus. Patients typically present with new localized pain that is burning and aching in quality, progressive in nature, and increases in severity and frequency over days to weeks. Focal deficits, such as weakness, numbness, and areflexia, develop over weeks or months.

Cervical Plexus

The cervical plexus, composed of the anterior rami of C1 to C4 cervical roots, innervates most neck muscles and provides sensory innervation to the anterior and lateral neck. Cervical plexopathy commonly occurs as a result of direct invasion from contiguous neck soft tissue tumors or indirectly from regional lymph node metastases from head and neck squamous cell carcinomas, lymphoma, or lung and breast adenocarcinomas. Involvement of the cervical plexus is less common than the brachial or lumbosacral plexus.

Patients with metastases of the cervical plexus typically complain of pain within the submandibular and subglottic area, posterior or lateral neck, or around the shoulder. Coughing, neck movement, or assuming a recumbent position exacerbates the pain. Sensory loss commonly develops along the C2, C3, and C4 dermatomal distribution. This is in contrast to sensory loss from surgical neck dissection, which occurs in the distribution of the superficial branches of the greater auricular nerve or transverse cervical branches. Involvement of the distal spinal accessory nerve produces partial trapezius and sternocleidomastoid weakness. Paralysis of the hemidiaphragm, causing dyspnea when supine or upon exertion, results from phrenic nerve involvement.

Brachial Plexus

The anterior rami of the lower four cervical and first thoracic nerve roots form the brachial plexus, providing motor and sensory innervation to most of the upper limb except the trapezius muscle and area of skin near the axilla. The lower trunk (C8 and T1) is closely related to the axillary lymph nodes and is most often involved in metastatic cancer. The upper trunk (C5–6) is free of lymph nodes and is less frequently affected. However, primary head and neck squamous cell carcinoma can invade the brachial plexus from above, affecting the upper plexus preferentially. Brachial plexopathy occurs in 0.43 percent of cancer patients, with breast and lung carcinomas being the most common associated malignancies. Melanoma, non-Hodgkin lymphoma, Burkitt lymphoma, renal cell carcinoma, and testicular seminoma are other less common sources.[16]

Pain is the most common presenting symptom of metastatic brachial plexopathy, and is moderate-to-severe in intensity, beginning in the shoulder girdle and radiating to the elbow, medial side of the forearm, and the fourth and fifth fingers, often exacerbated by shoulder movement. Focal weakness, atrophy, or sensory changes in the distribution of the C7 to T1 dermatomes are common. Involvement of the inferior trunk and medial cord of the brachial plexus from a carcinoma of the lung apex results in the superior sulcus or Pancoast syndrome; patients present with pain and numbness along the ulnar border of the hand and forearm, intrinsic hand muscle weakness, and a palpable mass in the supraclavicular area or axilla. Tumors located near the T1 nerve root involving the stellate ganglion may result in ipsilateral

Horner syndrome, which occurs in 25 percent of patients with Pancoast syndrome. Lymphedema secondary to lymphatic obstruction is present in 17 percent.[16]

Lumbosacral Plexus

The lumbar plexus is formed from the anterior rami of the T12 to L4 nerves, while nerve roots from L4 to S3 merge to form the sacral plexus. These plexuses supply motor and sensory innervation to the lower extremities and parts of the pelvis. Metastatic involvement of the lumbosacral plexus occurs in 0.71 percent of cancer patients. Tumors within the abdomen and pelvis may directly infiltrate the lumbosacral plexus, and the most common responsible tumors are cervical, uterine, colorectal, bladder, and prostate carcinomas, retroperitoneal sarcomas, and lymphomas. Tumors that commonly metastasize to the lumbosacral plexus are cancers of the breast and lung and lymphoma. Perineural spread of prostate cancer to the lumbosacral plexus has been reported rarely.[16]

More than 90 percent of patients with lumbosacral plexopathy present with pain. Lumbar plexus involvement results in pain in the costovertebral angle, whereas involvement of the lower sacral plexus causes pain in the hip and buttock, or radiating pain in the ipsilateral lower extremity. Pain is worsened by Valsalva maneuver, prolonged weight bearing, ambulation, sitting, or supine positioning. Motor and sensory loss develops in 60 percent of patients. The most common clinical signs are leg weakness (86% of these patients), sensory loss (73%), areflexia (64%), and leg edema (47%). Up to 25 percent of patients suffer from incontinence or impotence, which usually signifies bilateral and sacral involvement.

DIAGNOSTIC STUDIES

MRI is the neuroimaging study of choice for neoplastic plexopathy, typically showing a mass adjacent to the plexus or evidence of metastatic infiltration with hypointensity on T1-weighted imaging, hyperintensity on T2-weighted imaging, and gadolinium enhancement. These MRI findings are nonspecific and may occur in both metastatic and radiation plexopathy. The finding of linear or nodular enhancement along the nerves favors plexus metastases, while a thin "tram track" pattern of enhancement is associated with radiation-induced plexopathy.[17] Electrophysiologic studies can demonstrate the degree, type, and distribution of plexus involvement. Electromyography is helpful in delineating metastatic from radiation plexopathy, as myokymic discharges are common in the latter. Nerve conduction studies reveal variable axonal loss in both types of plexopathy, but patients with radiation plexopathy may also show signs of focal conduction block. FDG-PET studies aid in distinguishing neoplastic disease from radiation plexopathy—in metastatic disease there is increased uptake in the involved region whereas radiation plexopathy is typically hypometabolic. Nevertheless, normal neuroimaging and electrophysiologic studies do not always exclude a metastatic plexopathy.

DIFFERENTIAL DIAGNOSIS

Radiation plexopathy is the main differential diagnosis to consider in patients with suspected metastatic plexopathy. The incidence of radiation-induced brachial plexopathy in women with breast carcinoma is 1.8 to 9 percent, with 5 percent having disabling symptoms. Typically, radiation plexopathy develops from 0.5 to 20 years after treatment when the brachial plexus is affected, and 1 to 5 years after treatment with lumbosacral involvement. The risk of radiation plexopathy increases with radiation dose; the tolerance dose for brachial plexus (5 percent risk at 5 years) is 60 Gy for conventional fractionation regimens. Mechanisms of radiation injury include direct toxic effects on axons and indirect damage from fibrosis or fibrinoid necrosis within the vasa nervorum, resulting in microinfarctions. Usual presentations of radiation plexopathy include paresthesias and hypesthesia, followed by weakness and amyotrophy. In contrast to metastatic plexopathy, pain is usually mild and follows the sensory symptoms; the lower trunk of the brachial plexus is less likely to be involved as it is protected by the clavicle during radiation therapy. Horner syndrome is similarly uncommon, whereas lymphedema is more common than in metastatic plexopathy. Bilateral lumbosacral plexopathy is most likely due to radiation injury rather than neoplastic involvement. The presence of myokymic discharges on electrophysiologic studies strongly supports the diagnosis of radiation-induced plexopathy, which is present in up to 60% of patients. MRI generally reveals hypointensity on T1- and T2-weighted sequences, reflecting fibrosis without nerve enhancement; however, fibrotic changes with substantial inflammation can demonstrate both hyperintensity on T2-weighted images and contrast enhancement.[16,17]

Other differential diagnoses include plexopathy from intra-arterial chemotherapy, diabetes, infection, and hemorrhage, as well as infectious and paraneoplastic syndromes.

TREATMENT AND PROGNOSIS

The prognosis for most patients with metastatic plexopathy is generally poor because of the presence of advanced disease, and the primary therapeutic goal is palliation of symptoms. Aggressive pain management and prevention of complications of immobility are the focus of treatment. Radiation therapy can control local tumor growth, providing pain relief in 46 percent of patients with neoplastic brachial plexopathy and 85 percent of those with lumbosacral plexopathy. Intra-arterial chemotherapy has limited use in the treatment of intractable pain due to plexopathy, and paradoxically can also cause plexopathy. A multimodal approach in treating cancer pain should utilize opiate analgesics, infusion pumps, local and regional blocks, sympathetic ganglionic blocks, and epidural anesthetics. Dysethesias and paresthesias can be managed with transcutaneous nerve stimulation, tricyclic antidepressants, gabapentin, lamotrigine, topiramate, carbamazepine, phenytoin, and valproic acid. Rhizotomy and neurotractomy may be used in selected cases of chronic pain. Physical and occupational therapy and decreasing lymphedema by using compressive devices and diuretics can also be beneficial.

Radiation-induced malignancies (e.g., sarcomas) and atypical peripheral nerve sheath tumors develop rarely in patients with metastatic plexopathy treated with radiation. These neoplasms may appear from 4 to 41 years after radiation treatment, presenting as painful masses and leading to progressive neurologic deficits. Genetic conditions such as neurofibromatosis type 1 or ataxia-telangiectasia may predispose to these tumors. Patients with radiation-induced sarcomas warrant surgical excision with adjuvant chemoradiotherapy, whereas surgical resection is the main treatment for radiation-induced peripheral nerve sheath tumors.[16]

Peripheral Nerves

DEFINITION AND EPIDEMIOLOGY

Metastases to the peripheral and cranial nerves are relatively rare. Peripheral nerve dysfunction in cancer patients is commonly due to effects of chemotherapy, as is discussed in Chapter 28.

MECHANISMS, CLINICAL FEATURES, AND DIAGNOSIS

Peripheral nerves may be involved through extension or compression from adjacent bony or soft tissue structures such as the skull base, vertebrae, pelvis, lymph nodes, muscles, connective tissue, or nearby organs. Ulnar nerves may be affected by tumors at the elbow or axilla, radial nerves from the humerus, intercostal nerves by rib metastases, sciatic nerves from the bony pelvis, and fibular (peroneal) nerves behind the fibular head. Tumor invasion or metastasis to the mediastinal lymph nodes can cause hoarseness and vocal cord paralysis from involvement of the recurrent laryngeal nerve. Breast, prostate, lung, kidney, and thyroid cancers are the most common cause of peripheral nerve involvement. The recurrent laryngeal nerve, phrenic nerve, and cervical sympathetic nerves may be affected in lung cancers. Patients commonly present with severe, lancinating pain. Focal weakness, numbness, fasciculations, cramping, muscle atrophy, and reflex loss can help localize the involved peripheral nerve. Tinel sign and local tenderness can be elicited at the site of metastasis.

Metastases from solid tumors within the peripheral nerves themselves are exceedingly rare. Intraneural metastases resembling multiple neuropathies were reported in a patient with carcinoid tumor. Increasing pain, numbness, and weakness relating to the involved nerves are the usual presenting symptoms. Hematogenous spread to the posterior root ganglia has been reported in patients with colon and lung carcinoma.[16]

Occlusion of nerve vessels from ischemia is another mechanism for nerve injury from tumors such as intravascular lymphoma, a rare, high-grade, extranodal non-Hodgkin lymphoma with a tropism for the endothelium, commonly affecting the CNS and skin. Infiltration of lymphoma cells into the peripheral nervous system is referred to as neurolymphomatosis and signifies local invasion occurring outside the arachnoid investment of the nerves. This mechanism is distinct from infiltration associated with subarachnoid seeding from perineural tumors seen in epidural lymphoma. The malignant lymphocytes in neurolymphomatosis are clustered in perivascular sites, in contrast to meningeal lymphoma where the lymphocytes are in the epineurium. Large B-cell lymphoma is the most common cause; less frequent are T-cell, natural killer cell, and Hodgkin lymphomas. The average age at diagnosis of neurolymphomatosis is 55.5 years; 60 percent of patients are male.

Four patterns of presentations have been identified in patients with neurolymphomatosis: painful involvement of nerves or roots, cranial neuropathy with or without pain, painless involvement of peripheral nerves, and painful or painless involvement of a single peripheral nerve. The lumbosacral roots and cauda equina are the most common sites of involvement in the peripheral nervous system. Neurologic dysfunction usually antedates discovery of systemic lymphoma and is responsive to corticosteroids. Clinical findings suggesting neurolymphomatosis rather than paraneoplastic or inflammatory processes include severe pain, asymmetric distribution, and rapid evolution. MRI reveals enhancement or T2-weighted hyperintensity within the peripheral nerves. PET-CT is helpful in visualizing the involved nerve, which demonstrates hypermetabolism when the lesion is sufficiently large. Electrophysiologic studies reveal areas of demyelination at the site of lymphoma cell infiltration with axonal degeneration distally. CSF examination may be normal or may show increased protein concentration or a pleocytosis; these findings may be confused with acute or chronic inflammatory demyelinating polyneuropathy. Malignant cells are identified in up to 40% of patients. Biopsy of a clinically affected nerve is the gold standard for diagnosis. Histopathologic findings show tumor cell infiltration of the endoneurium and perineurium, displaying B-cell-associated surface antigens (CD19 and CD20) with high-proliferation index. Although biopsy is sensitive, it still may be falsely negative despite widespread lymphomatous involvement of peripheral nerves. In these cases, integration of clinical information, imaging findings, morphologic data from neural and non-neural tissues, and CSF studies may be helpful in establishing the clinical diagnosis. The response to empiric treatment may also lead to the correct diagnosis.[16]

TREATMENT AND PROGNOSIS

Systemic chemotherapy addressing multiple sites of involvement together with focal radiotherapy may offer relief of symptoms. For neurolymphomatosis, treatment principles are similar to primary CNS lymphoma. Methotrexate treatment in patients with neurolymphomatosis may provide clinical improvement and at least partial radiographic improvement. Radiotherapy is indicated for drug-refractory localized lymphomatous aggregates. When treated promptly and properly, neurolymphomatosis carries a similar prognosis to primary CNS lymphoma.[16]

METASTASES TO MUSCLES

Epidemiology and Pathophysiology

Skeletal muscle metastases are a rare occurrence in patients with malignancy, despite the fact that skeletal muscle comprises 50 percent of total body mass. The prevalence of metastases to muscles in autopsy studies ranges from 0.03 to 17.5 percent, and a retrospective study demonstrated that 0.42 to 4.9 percent of oncologic patients had muscle metastases. The rarity of these metastases is due to a number of factors, including blood flow variability between resting and exercise states causing a reduction of tumor cell adherence to underlying tissues, skeletal muscles producing anticancer factors such as leukemia inhibitory factor and interleukin-6, skeletal muscle microvasculature having the biochemical ability to destroy the cancer cells, and the skeletal muscles removing lactic acid, which plays a role in neovascularization.[18]

The hypothesized mechanisms of metastases include hematogenous dissemination by arterial emboli or venous spread (especially through the Batson plexus), extension from intramuscular lymph nodes, or perineural spread. The most frequent primary tumors are genitourinary and gastrointestinal cancers and melanoma. Metastases are most commonly located in paravertebral, iliopsoas, gluteal, and intercostal muscles.[18]

Clinical Features

Most patients with skeletal muscle metastases are asymptomatic, and these metastases are found incidentally during staging. Local pain and swelling occur in 14 percent, usually in patients with large lesions with massive infiltration or destruction. Patients with psoas involvement may present with "malignant psoas syndrome" with fixed flexion of ipsilateral hip and knees. Painless palpable masses arise in 10 percent of patients.[18]

Diagnostic Studies

The advent of CT, MRI, and FDG PET has facilitated detection of skeletal muscle metastases. Different types of CT findings have been recognized, including focal intramuscular masses with homogeneous contrast enhancement, abscess-like intramuscular lesions, diffuse metastatic muscle infiltration, multifocal intramuscular calcification, and intramuscular bleeding. MRI with gadolinium is superior to CT both in diagnosis and in planning treatment. The majority of patients with skeletal muscle metastases demonstrate extensive peritumoral enhancement associated with central necrosis. The increasing use of FDG PET/CT for staging and follow-up has resulted in the detection of many unsuspected cases of skeletal muscle metastases, which show high tumor-to-background contrast resolution. Needle biopsy establishes the diagnosis definitively.[18,19]

Differential Diagnosis

Conditions that may mimic skeletal muscle metastases are muscle hemangioma, intramuscular ganglion, myxoma, ischiorectal bursitis, benign muscle calcifications such as myositis ossificans, calcific tendinitis, angiomatosis, systemic sclerosis, and calcific myonecrosis.[18]

Treatment and Prognosis

As most patients have widespread systemic disease, the prognosis is generally poor. The main goal of treatment is therefore palliation, and therapeutic options include radiotherapy or chemotherapy. Surgical excision is considered for lesions larger than 4 cm and recommended for rapidly expanding lesions or those producing neurologic deficits. Reports have shown effective control of local tumor recurrence after wide excision that includes the infiltrative borders of the tumor.[19]

CONCLUDING COMMENTS

Cancer can involve any part of the nervous system and lead to significant neurologic morbidity, at times representing a catastrophic event for patients with cancer. Knowledge of both common and rare manifestations of nervous system metastases aids clinicians in early recognition and proper localization. Distinguishing metastatic from nonmetastatic diseases such as those with infectious, inflammatory, and vascular etiologies or from complications of cancer therapy is imperative. The appropriate use of neurodiagnostic modalities such as MRI frequently assists in reaching a correct diagnosis. Clinicians should establish realistic therapeutic goals, including symptomatic treatment to maintain quality of life of these patients. A multidisciplinary approach involving neurologists, neuro-oncologists, medical oncologists, radiation oncologists, neurosurgeons, specialists in palliative care, and rehabilitation experts is necessary.

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CHAPTER

27

Paraneoplastic and Nonparaneoplastic Autoimmune Syndromes of the Nervous System

SAROSH R. IRANI

GENERAL CONSIDERATIONS
- Incidence
- Pathogenesis
- Diagnosis
  - *Antibodies*
- Treatment

SPECIFIC SYNDROMES
- Limbic Encephalitis
  - *Laboratory Findings*
  - *Pathology*
  - *Diagnosis*
  - *Treatment*
- Encephalomyelitis
- Hypothalamic Dysfunction
- Brainstem or Basal Ganglia Encephalitis
- Cerebellum
  - *Clinical Findings*
  - *Laboratory Evaluation*
  - *Pathology*
  - *Diagnosis*
  - *Treatment*
- Opsoclonus-Myoclonus
- Visual Loss
  - *Retinopathy*
  - *Optic Neuritis and Neuropathy*
- Spinal Cord Syndromes
  - *Myelitis*
  - *Stiff-Person Syndrome*
- Peripheral Nerve and Dorsal Root Ganglion Syndromes
  - *Autonomic Neuropathy*
  - *Neuromuscular Junction Syndromes*
  - *Peripheral Nerve Hyperexcitability (Neuromyotonia)*
- Muscle Syndromes

The term *paraneoplastic syndrome* is often used to refer to symptoms or signs resulting from dysfunction of organs or tissues caused by a cancer, but which are not a direct effect of invasion by the neoplasm or its metastases. Perhaps most accurately, the term is used in a restricted sense to describe specific neurologic disorders that occur with increased frequency in patients with certain cancers, and are not caused by invasion, infection, systemic metabolic disorders, vascular disease, or side effects of cancer therapy. Paraneoplastic syndromes may affect virtually any organ or tissue (Table 27-1), including multiple regions within the nervous system (Table 27-2). These disorders, also termed *remote effects of cancer on the nervous system*, detailed in Table 27-3, are typically immune mediated, and encompass a clinically and pathologically more restricted group of disorders than the other nonmetastatic effects of cancer.[1,2] In addition to paraneoplastic immune-mediated disorders, this chapter addresses the increasingly recognized group of immune-mediated neurologic syndromes which have similar clinical features to the more traditionally recognized paraneoplastic syndromes but occur without an associated cancer.[3,4] These nonparaneoplastic immune-mediated syndromes are important to understand as they are often more responsive to immunotherapies than their closest counterpart paraneoplastic conditions.

GENERAL CONSIDERATIONS

Incidence

Several studies have addressed the frequency of paraneoplastic and nonparaneoplastic syndromes. Wide-ranging estimates from these studies are due to: (1) varied definitions; (2) the rigor used to exclude other causes of neurologic dysfunction; (3) the care with which the neurologic evaluation was performed; and (4) biases introduced by referral patterns. For example, the Lambert–Eaton myasthenic syndrome (LEMS) occurs in 3 percent or less of patients with small cell lung cancer (SCLC), but about 50 percent

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TABLE 27-1 ■ Selected Non-Neurologic Paraneoplastic Syndromes

General Physiologic (Host-Reactive) Syndromes

Fever
Anorexia and cachexia
Fatigue and "weakness"
Dysgeusia

Hematologic and Vascular Syndromes

Anemia
Leukemoid reaction
Eosinophilia, basophilia
Thrombocytosis
Thrombocytopenia
Hypercoagulability (Trousseau syndrome)
Erythrocytosis
Hyperviscosity

Skin and Connective Tissue Syndromes

Acanthosis nigricans
Tripe palms
Erythemas
Pruritus
Vasculitis
Flushing
Sweet syndrome
Ichthyosis
Hypertrichosis
Pachydermoperiostosis
Melanosis, vitiligo

Endocrine-Metabolic Syndromes

Cushing syndrome
Hypoglycemia and hyperglycemia
Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Carcinoid syndrome
Hypercalcemia and hypocalcemia
Systemic nodular panniculitis
Acromegaly
Gynecomastia
Hypernatremia

Gastrointestinal Syndromes

Protein-losing enteropathy
Malabsorption
Exudative enteropathy
Zollinger–Ellison syndrome

Collagen-Vascular Syndromes

Arthritides
Scleroderma
Lupus erythematosus
Amyloidosis
Palmar fasciitis

Renal Syndromes

Glomerulonephritis
Nephrotic syndrome
Renal failure
Hypokalemia

Bone Syndromes

Hypophosphatemic osteomalacia

Pulmonary osteoarthropathy

Clubbing
Synovitis

TABLE 27-2 ■ Nonmetastatic Complications of Cancer on the Nervous System

Disorder	Example(s)
Vascular disorders	Hemorrhage/infarction
Infections	Meningitis/abscess
Nutritional disorders	Wernicke encephalopathy
Metabolic disorders	Hypocalcemia
Side effects of therapy	
Surgery and other diagnostic or therapeutic procedures	Meningitis/CSF leak
Radiation therapy	Brain/spinal cord necrosis
Chemotherapy/small molecules	Peripheral neuropathy
Biologic therapy	PML
"Remote" or paraneoplastic syndromes	(see Table 27-3)

CSF, Cerebrospinal fluid; PML, progressive multifocal leukoencephalopathy.

of SCLC patients have either subjective or objective muscle weakness. While less than 10 percent of cancer patients had a "neuromyopathy" on physical examination, abnormalities of peripheral nerve function were found by quantitative sensory testing in nearly half. Myopathic changes are found on muscle biopsy in one-third of patients with lung cancer. These neurologic symptoms can predate the detection of cancer; in patients with peripheral sensory neuropathy of unknown cause, for instance, nearly one-third in some studies developed cancer within 6 years.

True incidence figures for paraneoplastic syndromes are rare. Population-based data are available for myasthenia gravis, LEMS, and dermatomyositis. A total of 5 percent of myasthenia gravis patients have a paraneoplastic form. In another study, the annual incidence of LEMS was rare (0.4 per million persons), but was equally divided between those with SCLC and those with nonsmall cell lung cancer (NSCLC). For dermatomyositis, the overall age- and sex-adjusted incidence is around 10 per million persons; 20 percent have cancer. Nearly one-fifth in one study suffered from the amyopathic subtype (rash but no muscle weakness).

Other studies have addressed the percentage of patients with a given tumor likely to have a paraneoplastic syndrome. Myasthenia gravis occurs in 10 to 15 percent of patients with thymoma. LEMS has been found in about 3 percent of patients with lung cancer. Paraneoplastic peripheral neuropathy occurs in

TABLE 27-3 ■ Neurologic Paraneoplastic Syndromes

Brain

- Limbic encephalitis*
- Encephalomyelitis*
  - Hypothalamic encephalitis
  - Brainstem/basal ganglia encephalitis
- Cerebellar degeneration*
- Opsoclonus myoclonus*
- Visual loss
  - Carcinoma/melanoma retinopathy*
  - Optic neuropathy

Spinal Cord

- Myelitis/myelopathy
  - Demyelinating myelopathy
    - Neuromyelitis optica
  - Necrotizing myelopathy
- Motor neuron syndromes
  - Subacute motor neuronopathy
  - Amyotrophic lateral sclerosis (ALS)
- Stiff-person syndrome

Peripheral Nerve/Dorsal Root Ganglia

- Subacute sensory neuronopathy*
- Chronic/subacute sensory or sensorimotor neuropathy
- Autonomic neuropathy*
- Acute sensorimotor neuropathy (Guillain–Barré syndrome)
- Plexitis (e.g., brachial neuritis)
- Vasculitic neuropathy
- Association with plasma cell dyscrasias

Neuromuscular Junction

- Lambert–Eaton myasthenic syndrome*
- Myasthenia gravis*
- Neuromyotonia

Muscle

- Dermatomyositis*
- Polymyositis
- Inclusion-body myositis
- Necrotizing myopathy
- Cachectic myopathy
- Myotonia

*Indicates "classic" paraneoplastic syndrome.

10 percent of malignant monoclonal gammopathies, and in 50 percent of patients with osteosclerotic myeloma. Most known paraneoplastic syndromes are so uncommon that exact incidence figures cannot be established, but they probably occur in less than 0.01 percent of cancer patients.

A higher yield is found when patients whose symptoms suggest the possibility of a paraneoplastic syndrome have serum and cerebrospinal fluid (CSF) sent for examination for paraneoplastic antibodies. Using this approach, one-fourth of consecutive patients examined over 2 years have well-defined antineuronal autoantibodies.

Pathogenesis

Although the exact pathogenesis of most paraneoplastic syndromes has not been established, the consensus is that most, or perhaps all, neurologic paraneoplastic syndromes are immune-mediated. Evidence for this hypothesis includes the presence of autoantibodies that recognize antigens present in both the cancer and the normal nervous system. Some of these so-called paraneoplastic or onconeural antigens are also expressed in normal testes, an organ that, like the brain, is an immunologically privileged site. If the antigen cannot be identified in a cancer with a known serum paraneoplastic antibody, it may be that either the patient does not have a paraneoplastic syndrome or that some other cancer is present and caused the disorder. Examination of the CSF of patients with paraneoplastic syndromes involving the central nervous system (e.g., limbic encephalitis) usually reveals a pleocytosis, at least early in the course of the disease, with a persistently slightly elevated protein level, an increased IgG Index, and oligoclonal bands. Some of these oligoclonal bands in the CSF have been identified as paraneoplastic antibodies themselves. The relative specific level of the paraneoplastic antibody (expressed as a concentration of antibody against total IgG) is substantially higher in CSF than in the serum. This indicates that the antibody was synthesized by B cells within the central nervous system (CNS), rather than simply diffusing across the blood–brain barrier. The tumors of patients with paraneoplastic syndromes, although identical in histologic type to tumors of patients without neurologic features, are more likely to be infiltrated with inflammatory cells including T cells, B cells, and plasma cells.[5] The nervous system is usually also infiltrated by inflammatory cells, and some paraneoplastic syndromes respond to treatment with immunosuppression.

The current concept of the pathogenesis of paraneoplastic syndromes is that the tumor ectopically expresses an antigen that is normally expressed in the nervous system. Onconeural antigens are present in the tumors of all patients with antibody-positive paraneoplastic syndromes. In some tumors, such as SCLC, onconeural antigens are present in all tumors, even in those patients who do not develop paraneoplastic antibodies or a paraneoplastic syndrome. The onconeural antigen in the tumor cell is probably recognized by the immune system when tumor cells spontaneously undergo apoptosis and the apoptotic bodies containing the antigen are phagocytized by antigen-presenting cells. Current evidence conflicts as to whether the antigens in the tumor are mutated or identical in structure to normal neural antigens. The former would provide a mechanism for loss of tolerance, leading to development of paraneoplastic antibodies. The body's immune system attacks structures expressing the paraneoplastic antigen, resulting in two effects. First, the immune attack may control the growth of the tumor and in rare instances obliterate it. Second, the immune response also attacks the nervous system itself; both B and T cells can be found in the CNS of patients with CNS paraneoplastic syndromes. The B cells generally reside in the perivascular spaces and the T cells in both perivascular spaces and in the brain parenchyma. Often the granzyme-B-expressing cytotoxic T cells are closely opposed to neurons. Further, the T cells found in the nervous system are either mono- or oligoclonal and respond only to a specific antigen. Hence, these diseases appear to be T-cell driven.

By contrast, consensus suggests that autoantibodies which target the native extracellular domains of neuronal proteins are far more likely to be directly pathogenic, as they are likely to access their target antigen in vivo.[3,6] Indeed, two paraneoplastic syndromes with antibodies that target the extracellular domains of proteins expressed at the human neuromuscular junction, LEMS and myasthenia gravis, were the first to meet formal criteria for an antibody-mediated autoimmune disease. Other paraneoplastic syndromes in which antibodies likely play a causal role include NMDA receptor antibody-associated encephalitis, CASPR2 antibody-associated Morvan syndrome, AMPAR-associated encephalitis, and autonomic neuropathy with antibodies to the ganglionic acetylcholine (ACh) receptor. In addition, a variety of syndromes with autoantibodies that target the extracellular domains of native neuroglial surface proteins have no tumor associations. These include autoantibodies against leucine-rich glioma inactivated 1 (LGI1), Iglon5, the $GABA_A$ receptor, aquaporin-4 (AQP4), and myelin oligodendrocyte glycoprotein (MOG).

Diagnosis

Recommended criteria for the diagnosis of a neurologic paraneoplastic syndrome are listed in Table 27-4.[7] Alternative causes that might explain the clinical symptoms must be excluded. "Classic" refers to those neurologic disorders characteristic of a paraneoplastic syndrome as indicated in Table 27-5. Hence, a clear clinical definition of the syndrome is required. "Onconeural" refers to antibodies that recognize antigens that are restricted to the nervous system (or testes) and to some cancers. Originally, when the antigens were unknown, two separate nomenclatures were devised to designate these antibodies. The nomenclature applied at Memorial Sloan-Kettering Cancer Center (e.g., Yo, Hu) refers to the first two letters of the last name of the index patient while the Mayo Clinic terminology (e.g., anti-PCA-1, anti-ANNA-1) refers to the staining pattern by immunohistochemistry. In Table 27-5 the latter system is identified in parentheses. Once these antigens have been identified, the antigen's name is used to designate the antibody in question (e.g., NMDAR antibody). The term "well-characterized" refers to an antibody whose antigen has been robustly identified, typically by multiple laboratories.

TABLE 27-4 ■ Diagnostic Criteria for Paraneoplastic Neurologic Syndromes (PNS)

Definite PNS

1. A classic syndrome and cancer that develops within 5 y of the diagnosis of the neurologic disorder.
2. A nonclassic syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy provided that the syndrome is not susceptible to spontaneous remission.
3. A nonclassic syndrome with onconeural antibodies (well-characterized or not) and cancer that develops within 5 y of the diagnosis of the neurologic disorder.
4. A neurologic syndrome (classic or not) with well-characterized onconeural antibodies (e.g., anti-Hu, Yo, CV2, Ri, Ma-2, or amphiphysin), and no cancer.

Possible PNS

1. A classic syndrome, no onconeural antibodies, no cancer but at high risk to have an underlying tumor.
2. A neurologic syndrome (classic or not) with partially characterized onconeural antibodies and no cancer.
3. A nonclassic syndrome, no onconeural antibodies, and cancer present within 2 y of diagnosis.

From Graus F, Delattre JY, Antoine JC, et al: Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 75:1135, 2004, with permission.

The 5-year period identified in the criteria for the development of cancer is reasonable but problematic. Although in most patients with a paraneoplastic syndrome the cancer is identified within a year or so, in an occasional patient, even when the neurologic syndrome and the antibody clearly have been

TABLE 27-5 ■ The Major Antibody-Associated Neurologic Paraneoplastic and Nonparaneoplastic Disorders

Antibody Target	Location	Antigen/Gene(s)	Extracellular or Intracellular Epitope	Usual Tumor or Site of Origin	Neurologic Disorder
Antibody Markers of Neurologic Paraneoplastic Syndromes, Requiring a Search for Tumor					
Hu (ANNA-1)	Nucleus > cytoplasm (all neurons)	HuD (Elavl4); Elavl2, 3	Intracellular	SCLC, neuroblastoma, prostate	PEM, PSN, autonomic dysfunction
Yo (PCA-1)	Cytoplasm, Purkinje cells	CDR2, CDR2L	Intracellular	Ovary, breast, lung	PCD
Ri (ANNA-2)	Nucleus > cytoplasm (CNS neurons)	Nova 1,2	Intracellular	Breast, gynecologic, lung, bladder	Ataxia/opsoclonus, brainstem encephalitis
CRMP5 (CV2)	Cytoplasm, oligodendrocytes, neurons		Intracellular	SCLC, thymoma	PEM, PCD, chorea, optic, sensory neuropathy
Ma2 (ANNA-3)	Neurons (nucleolus)		Intracellular	Testis	Limbic, brainstem (diencephalic) encephalitis
Amphiphysin	Presynaptic		Intracellular synaptic	Breast, SCLC	SPS
Sox-1 (AGNA-1)	Nucleus of Bergman glia, other neurons		Intracellular	SCLC	LEMS
Tr (PCA-Tr)	Cytoplasm, dendrites of Purkinje cells	DNER	Intracellular	Hodgkin	PCD
Recoverin	Photoreceptor, ganglion cells	Recoverin	Intracellular	SCLC	CAR
Antibodies Associated With Neurologic Dysfunction That Do Not Always Require a Search for Cancer					
AChR	Postsynaptic NMJ (electron immunohistochemistry)	AChR	Extracellular	Thymoma	MG
VGCC	Presynaptic NMJ	P/Q VGCC	Extracellular	SCLC	LEMS
NMDAR	Neuronal cell surface, hippocampus, other brain regions	NR1 subunit	Extracellular	Ovarian teratoma	Encephalitis
AMPAR	Neuronal cell surface	GluR1,2 subunits	Extracellular	Thymoma, breast, lung	LE
AChR	Postsynaptic NMJ	Skeletal muscle AChR	Extracellular	Thymoma	MG
nAChR	Postsynaptic ganglia	Ganglionic α3 subunit	Extracellular	SCLC, thymoma	Autonomic neuropathy
LGI1	Neuropil	LGI1	Extracellular, secreted molecule	Thymoma, rarely	LE
CASPR2	Neuropil and juxtaparanode		Extracellular	Thymoma	Peripheral nerve hyperexcitability, Morvan syndrome
GAD	Purkinje cell cytoplasm, nerve terminals, other neurons	Glutamic acid decarboxylase 65 and 67	Intracellular	Several (renal, Hodgkin, SCLC)	SPS, cerebellar ataxia
Glycine receptor	Brainstem, spinal cord neurons	α1 subunit	Extracellular	Lung	PERM
$GABA_A$R	Neuronal surface	α1/B3/y2 subunits	Extracellular	?	SPS

(Continued)

TABLE 27-5 ■ (Continued)

Antibody Target	Location	Antigen/Gene(s)	Extracellular or Intracellular Epitope	Usual Tumor or Site of Origin	Neurologic Disorder
$GABA_BR$	Neuronal surface	B1/2 subunits	Extracellular	SCLC	LE
MuSK	Muscle	MuSK	Extracellular	Thymoma	MG
Antibodies in Neurologic Disorders From Single Case Reports or Small Series. Some Are Paraneoplastic					
PCA-2	Purkinje cytoplasm and other neurons		Intracellular	SCLC	PCD
Ma	Neurons (subnucleus)	Ma1 and Ma2	Intracellular	Lung, others	PEM, brainstem
ANNA 3	Nuclei, Purkinje cells		Intracellular	Lung	Sensory neuronopathy, PEM
mGluR1, mGluR5	Purkinje cells, Olfactory neurons, hippocampus	Metabotropic glutamate receptors	Extracellular	Hodgkin	PCD
Kelch-like protein 11	Multifocal	KLHL11	Intracellular	Testicular seminoma	Encephalitis
PDE10A	Basal ganglia		Intracellular	Varied	Varied
Zic4	Nuclei of cerebellar		Intracellular	SCLC	PCD
PKC-gamma	Purkinje cells		Intracellular	NSCLC	PCD
Gephyrin	Postsynaptic membranes		Intracellular	Unknown primary	SPS
Synaptotagmin	Presynaptic junction		Intracellular, vesicle protein	?	LEMS
Synaptophysin	Presynaptic junction		Intracellular, vesicle protein	SCLC	Neuropathy
BRKSK2	Neuronal cytoplasm		Intracellular	SCLC	LE
Adenylate kinase 5	Neuronal cytoplasm		Intracellular	Nil	LE
CARP VIII	Purkinje cells		Intracellular	Melanoma	PCD
Homer 3	Neuropil, cerebellum		Intracellular	None known	PCD
Aquaporin 4	Astrocyte foot process	M23 > M1 isoform	Extracellular	Rare	Neuromyelitis optica

CAR, cancer associated retinopathy; LE, limbic encephalitis; LEMS, Lambert-Eaton myasthenic syndrome; PCD, paraneoplastic cerebellar degeneration; PEM, paraneoplastic encephalomyelitis; PERM, progressive encephalomyelitis with rigidity and myoclonus; PSN, paraneoplastic sensory neuropathy; MG, myasthenia gravis; SPS, stiff person syndrome.

recognized, more than 5 years may elapse before the cancer is found. The inability to find a cancer, even after 5 years, does not mean that the patient does not have a paraneoplastic syndrome. There are rare, but well-documented, cases of a paraneoplastic syndrome being associated with spontaneous remission of a cancer.[8] Also, there are occasional patients with high-titer, well-characterized paraneoplastic antibodies who almost certainly never have had nor will develop a cancer.

The only unequivocal method of determining whether a given patient has a paraneoplastic syndrome is by identifying an autoantibody that reacts with the portion of the nervous system suffering damage and a neoplasm whose cells express the same antigen. If the antigen is not found in the neoplasm, the patient either does not have a paraneoplastic syndrome or has another cancer—as yet unfound—that expresses the antigen, and a new search should be considered.

Several clinical features can assist in the diagnosis. Most paraneoplastic syndromes develop rapidly, progress over weeks to months, and then stabilize; syndromes that begin insidiously or are characterized by exacerbations and remissions are less likely to be paraneoplastic. Many paraneoplastic syndromes result in serious neurologic disability although those with antibodies to neuronal surface epitopes are often responsive to immunotherapies. Paraneoplastic syndromes affecting the CNS are typically associated with an inflammatory CSF, including pleocytosis, elevated levels of protein, increased CSF immunoglobulins, and unique oligoclonal bands; one of these features is present in nearly all patients with a CNS paraneoplastic syndrome. Magnetic resonance imaging (MRI) may be normal or have abnormalities consistent with the clinical findings (e.g., medial temporal lobe T2-weighted hyperintensity in patients with limbic encephalitis or cerebellar atrophy in patients with paraneoplastic cerebellar degeneration). When the MRI is normal, fluorodeoxyglucose positron emission tomography (PET) scans may reveal hypometabolism in the brain that is either diffuse or focal, although these findings are nonspecific. Several of the paraneoplastic syndromes (e.g., LEMS) are so stereotypic that the correct diagnosis can be strongly suspected even before additional diagnostic testing has excluded alternative diagnoses.

ANTIBODIES

Many paraneoplastic syndromes are characterized by serum and CSF autoantibodies which react with both the areas of the nervous system involved and the underlying cancer. Some autoantibodies (e.g., Hu, Ri, and Yo antibodies) are highly specific for the presence of an underlying cancer and strongly suggest a specific cancer that can guide workup. For example, the Yo antibody is strongly associated with breast and gynecologic tumors and requires careful mammography as well as pelvic imaging. However, some paraneoplastic syndromes can be caused by many tumors, and therefore a more widespread search including total-body computed tomography (CT) or PET scan is frequently appropriate. Table 27-5 lists many of the antibodies that can be found in the serum of patients with paraneoplastic syndromes. Other autoantibodies (e.g., ACh receptor antibodies), however, are found in patients both with and without cancer. It is usually not necessary to measure antibodies in the CSF of patients in whom serum antibodies are negative. Yet, in the case of a few autoantibodies, since serum has a high total IgG level which inherently increases the test background, it is often useful to study CSF in conjunction. This is supported by the observation that patients with CNS paraneoplastic syndromes often show a higher relative concentration of the autoantibody in CSF than serum, indicating its intrathecal synthesis.

Most paraneoplastic antibodies are usually associated with specific paraneoplastic syndromes and a limited number of implicated cancers (Table 27-5). For example, the Hu-antibody is more likely to cause encephalomyelitis and is usually associated with SCLC, whereas the CRMP5 antibody is more likely to be associated with cerebellar ataxia, chorea, optic neuritis, uveitis, and LEMS. Both of these antibodies are associated with SCLC, but only the CRMP5 antibody is associated with thymoma. Regardless of the tumor type, patients with the CRMP5 antibody survive significantly longer, a finding that does not appear to be related to a less severe neurologic disorder than those patients with the Hu antibody.

As discussed above, antigens can be divided into two groups: group 1 consists of intracellular antigens, either cytoplasmic or nuclear, and group 2 consists of antigens expressed on the surface of neurons whose extracellular domains are the autoantibody targets. This division identifies disorders that usually respond to treatment and in which antibodies are likely causal (group 2), and those that usually do not respond to treatment and where the pathogenesis is likely T-cell mediated (group 1).[6]

Group 1 antigens that usually are paraneoplastic, including Hu, Yo, and several others, may occur only occasionally in patients without cancer. In one series of Hu antibody positive patients, 3 percent with clinical follow-up of more than 3 years did not develop an identifiable cancer, and there was no clinical differences between those patients who did and did not develop cancer. One possible explanation is that a cancer was present but spontaneously regressed. Both spontaneous regression of the cancer and antineuronal antibodies are thought to be more common in infants with neuroblastoma. Group 1 also consists of intracellular antigens that are cancer-specific but not usually helpful in diagnosis, including Sox 1 and Zic. Other intracellular antigens are associated with autoimmune disorders of the nervous system that are only sometimes paraneoplastic, including glutamic acid decarboxylase (GAD). Indeed, some authors prefer to classify GAD and amphiphysin in a separate group of intracellular synaptic antigens, in recognition of the potential for these autoantibodies to access their targets upon vesicle fusion with the presynaptic membrane.

Group 2 antigens can be divided into those surface antigens associated with autoimmune CNS syndromes that are often associated with an underlying tumor, such as the AMPAR and $GABA_BR$, and those which are only sometimes paraneoplastic, including CASPR2 and the NMDAR. In addition, it is increasingly recognized that some cell surface targets have a very limited, if not absent, epidemiologic association with an underlying tumor; examples include LGI1 and Iglon5.[9]

Treatment

Overall, patients with autoantibodies to intracellular antigens respond less well to immunologic therapeutic interventions than those in group 2. Nevertheless, there are two general approaches to the treatment of paraneoplastic neurologic disorders. In many cases, effective therapy focuses on treatment of the underlying tumor. This aims to prevent progression of the disease and, in some instances, leads to improvement or, more rarely, complete amelioration of the neurologic symptoms. Effective treatment of the tumor may remove the inciting antigen and thus dampen the immune response causing the neurologic damage.

Because paraneoplastic syndromes are likely immune mediated, the second treatment approach is to suppress the immune response. Several different forms of immunosuppression, including corticosteroids, plasma exchange, intravenous immunoglobulin, cyclophosphamide, and cyclosporine or tacrolimus, have been used to treat paraneoplastic syndromes (Table 27-6). This immunosuppression does not appear to worsen the outcome of the tumor, and may sometimes associate with stabilization or improvement of the syndrome, especially if administered early.

Despite these interventions, many patients with autoantibodies against group 1 antigens show limited improvement. By contrast, patients with autoantibodies against cell surface-exposed epitopes (e.g., the NMDAR or LGI1) are highly likely to respond to immunotherapy, maybe in part since many such patients do not have an underlying cancer. Treatment outcomes in these patients can frequently be almost complete. With regard to a potential third group of autoantibodies that lie intracellularly within synapses (e.g., GAD and amphiphysin antibodies), the patients may or may not have cancer and may respond well to immunosuppression.

TABLE 27-6 ■ Treatment of Neurologic Paraneoplastic Syndromes

Syndrome	Treatment
*Syndromes That Usually Respond to Treatment**	
Lambert–Eaton myasthenic syndrome	IV immunoglobulin, plasma exchange, 2,3 diaminopyridine, immunosuppression[†]
Myasthenia gravis	IV immunoglobulin, plasma exchange, immunosuppression, anticholinesterases
Dermatomyositis	IV immunoglobulin, immunosuppression
Opsoclonus-myoclonus (pediatric)	IV immunoglobulin, corticosteroids, ACTH, rituximab
Neuropathy associated with osteosclerotic myeloma	Radiation, chemotherapy
NMDAR	First line: corticosteroids, IV immunoglobulin, plasma exchange; Second line: cyclophosphamide, rituximab
LGI1	Corticosteroids, IV immunoglobulin, plasma exchange
Encephalitis with cell surface antigens other than NMDAR and LGI1 (e.g., AMPA receptor, GABA$_{A/B}$ receptor, CASPR2)	Corticosteroids, IV immunoglobulin, plasma exchange, cyclophosphamide
*Syndromes That May Respond to Treatment**	
Stiff-person syndrome	IV immunoglobulin, rituximab, diazepam, baclofen
Neuromyotonia	IV immunoglobulin, plasma exchange, phenytoin, carbamazepine
Guillain–Barré/CIDP	IV immunoglobulin, plasma exchange
Vasculitis of nerve and muscle	Corticosteroids, cyclophosphamide
Opsoclonus-myoclonus (adults)	Corticosteroids, cyclophosphamide, protein A column, clonazepam, thiamine
MAG-antibody associated peripheral neuropathy (Waldenström macroglobulinemia)	IV immunoglobulin, plasma exchange, chlorambucil, cyclophosphamide, fludarabine, rituximab
Acute necrotizing myopathy	Immunosuppression

In all cases, treatment should also focus on identifying and treating the tumor. ACTH, adrenocorticotopic hormone; CIDP, chronic inflammatory demyelinating neuropathy; IV, intravenous.

*Syndromes that usually do not respond to treatment include encephalomyelitis, sensory neuronopathy, autonomic dysfunction, cerebellar degeneration, and cancer- and melanoma-associated retinopathy.

[†] Immunosuppression includes corticosteroids or azathioprine.

SPECIFIC SYNDROMES

Paraneoplastic syndromes that affect the nervous system are classified in Table 27-5. Only some of the more common syndromes are considered in this chapter, and more extensive reviews are available elsewhere.[1,3,5]

Limbic Encephalitis

Limbic encephalitis is characterized by the acute-to-subacute onset of short-term memory loss, seizures, and behavioral abnormalities. The disorder has been reported in association with a variety of tumors including SCLC and ovarian teratoma. A clinically identical autoimmune disorder occurs in patients without cancer, and both the paraneoplastic and nonparaneoplastic forms of limbic encephalitis are associated with a variety of different autoantibodies.

Limbic encephalitis can begin with seizures and changes in mood and personality. Accompanying features include severe impairment of recent memory with relatively preserved remote memory. Patients are often agitated and confused and can show a range of behavioral features from depression and agitation to a florid delirium. Symptoms can begin quite abruptly or the onset may be more gradual, occurring over several weeks to even a few months. When behavioral changes dominate the symptomatology, particularly when the disorder affects young women, a diagnosis of primary psychiatric disease may occur before a correct diagnosis is made.[10]

In addition to these features, patients may display other specific characteristics which can be highly suggestive, if not pathognomonic, of their underlying autoantibody. For example, patients with NMDAR-antibody encephalitis often exhibit a multifaceted psychiatric prodrome with features of both mood changes and psychosis, in addition to a complex movement disorder, dysautonomia, and coma.[10,11] By contrast, patients with LGI1 antibodies exhibit a prodrome of remarkably frequent focal seizures with semiologies including thermal sensations, piloerection, and synchronous spasms of the arm and face, termed faciobrachial dystonic seizures (FBDS).[9] The latter appear exclusive to patients with LGI1 antibodies. CASPR2 antibodies are associated with peripheral nerve hyperexcitability including Morvan syndrome, but some patients present with a pure encephalitis. CASPR2 antibodies may be associated with thymic tumors, especially in patients with peripheral nerve involvement.[12]

Laboratory Findings

The CSF is often inflammatory, at least early in the course of the disease, although this finding can be variable between autoantibodies. The MRI may be subtle or normal although abnormalities, particularly medial temporal lobe hyperintensities on the T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences (Fig. 27-1), are common. Electroencephalographic (EEG) findings include focal or generalized slowing and occasional epileptiform activity, particularly in the temporal areas. There are occasionally some more specific features: patients with LGI1 antibodies have especially frequent epileptiform discharges, often subclinical, and some of the more encephalopathic patients with NMDAR antibodies can have the EEG appearance termed "extreme delta brush." Measurement of brain metabolism with PET or single-photon emission computerized tomography (SPECT) scanning demonstrates abnormalities in the medial temporal lobes. The areas may be either hypermetabolic due to seizure activity or inflammation or may be hypometabolic late in the course, related to neuronal degeneration. Very recently, strong HLA associations have been associated with LGI1 and CASPR2 antibody encephalopathies. Given their robust nature, particularly in the era of personalized medicine, these tests are likely to be part of a clinical work up of these patients.

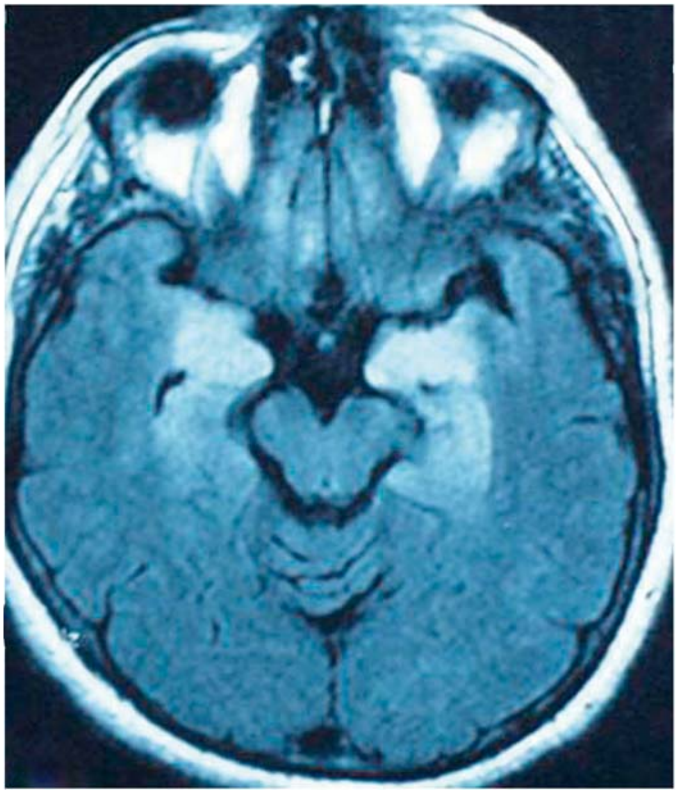

FIGURE 27-1 ■ Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) of a patient with paraneoplastic limbic encephalopathy. There is marked hyperintensity in the medial temporal lobes bilaterally. In addition, there is slight dilatation of the temporal horns, suggesting atrophy.

The most important diagnostic test is measurement of autoantibodies. The commonest antibodies found in paraneoplastic limbic encephalitis are those which target Hu (SCLC), Ma2 (testicular cancer), CRMP5/CV2 (SCLC-thymoma), the NMDAR (ovarian teratoma), and the $GABA_B$ receptor (SCLC). Antibodies found in patients who frequently do not have cancer include antibodies against LGI1, CASPR2, and the $GABA_A$ receptor.

PATHOLOGY

Typical limbic encephalopathy is characterized by the destruction of hippocampal neurons along with inflammatory infiltrates both in the perivascular spaces and in the brain parenchyma. In some patients, particularly those who die many years after the disorder begins, findings are consistent with sclerosis of the hippocampus, without inflammatory infiltrates, particularly in patients with Hodgkin disease. Whether inflammation was present at onset and disappeared over time is unclear. In fact, the literature has examples of a rapid evolution from limbic encephalitis to hippocampal sclerosis; this finding may have implications for a subset of patients with adult-onset medial temporal lobe epilepsy secondary to hippocampal sclerosis.

DIAGNOSIS

Overall, not accounting for nuances of the clinical presentation, two of the most important alternate diagnoses to consider are herpes simplex encephalitis and acute primary psychiatric presentations. Other diagnostic considerations include temporal lobe tumors, systemic lupus erythematosus, Hashimoto encephalopathy, human herpes virus type 6 (especially after bone marrow transplantation), and a variety of metabolic abnormalities causing delirium.

The other important diagnostic consideration is to differentiate paraneoplastic limbic encephalitis from nonparaneoplastic autoimmune limbic encephalitis. As these two disorders are often clinically indistinguishable, almost all patients require at least an initial search for an underlying neoplasm.

TREATMENT

Aside from treatment of the tumor, immunosuppression is the mainstay of therapy, similar to that for other paraneoplastic and autoimmune disorders. The earlier treatment is started, the more likely the illness will either stabilize or improve. Yet, in some of these disorders, particularly those associated with cell surface antibody targets, even late treatment of comatose patients may lead to significant resolution of the neurologic symptoms.

Encephalomyelitis

Paraneoplastic limbic encephalopathy may also occur as part of a more widespread disorder (encephalomyelitis) that is associated with carcinoma. The clinical presentation often includes subacute sensory neuronopathy, cerebellar degeneration, myelopathy, and sometimes peripheral neuropathy or myopathy; these disorders are discussed in other sections of this chapter.

Hypothalamic Dysfunction

Isolated paraneoplastic hypothalamic dysfunction is rare. The disorder usually occurs in conjunction with a more widespread encephalitis. Hypothalamic dysfunction characteristically occurs as a part of the syndrome in patients with Ma2 (Ta) antibodies and testicular cancer, CRMP5 (CV2) encephalomyelitis associated with thymoma, and NMDA receptor antibody encephalitis, associated with ovarian teratoma in around 20 percent of cases. The disorder is sometimes responsive to immunoglobulin therapy, and also occurs in children with neuroblastoma and sometimes in children without known cancer. Symptoms of hypothalamic dysfunction include somnolence, temperature dysregulation with hyperhidrosis, endocrinopathies including diabetes insipidus and hypothyroidism, narcolepsy or somnolence, weight gain, and loss of libido.

Brain MRI may reveal evidence of inflammation in the hypothalamus including contrast enhancement. Treatment consists of discovery and treatment of the underlying tumor as well as immunosuppression. Prognosis is dependent on the underlying clinical/serologic syndrome. For example, patients with testicular cancer and Ma2 antibodies sometimes stabilize and even improve, at least partially, but patients harboring other antibodies, such as Hu antibodies, do less well.

Brainstem or Basal Ganglia Encephalitis

Paraneoplastic brainstem encephalitis, characterized by the subacute development of bulbar, midbrain, or basal ganglia signs, usually occurs as part of the more diffuse syndrome of encephalomyelitis, although it sometimes presents as a dominant or isolated clinical finding. The syndrome usually affects the lower brainstem preferentially, causing diplopia, vertigo, oscillopsia, dysarthria, dysphagia, hypoventilation, hearing loss, facial weakness, myokymia, facial numbness, or opsoclonus in various combinations. When the upper brainstem or basal ganglia are affected, movement disorders including chorea, dystonia, bradykinesia, myoclonus, and parkinsonism may occur along with daytime sleepiness. The disorder has been associated with a number of antibodies including those against Hu (usually with more widespread encephalomyelitis symptoms), Ri (typically with opsoclonus), Ma2 (featuring prominent midbrain and diencephalic dysfunction), and the NMDA receptor (with central respiratory failure and coma). In patients with adult-onset autoimmune chorea, the disorder is paraneoplastic in over one-third; CV2/CRMP5 and Hu are commonly associated antibodies. Although yet to be confirmed by several laboratories, dopamine 2 receptor (D2R) antibodies have been described in children with a basal ganglia encephalitis and also in children with Sydenham chorea.

Cerebellum

Of the paraneoplastic disorders affecting the brain, paraneoplastic cerebellar degeneration is perhaps the most easily recognized and clinically the best described. It is characterized pathologically by loss of cerebellar Purkinje cells and is associated with several different cancers and autoantibodies.

CLINICAL FINDINGS

Paraneoplastic cerebellar degeneration was first described in 1919, but the association between it and cancer was not recognized until 1938. Paraneoplastic cerebellar degeneration can be associated with any malignancy, but the most common culprits include lung cancer (particularly SCLC), ovarian or uterine cancer, and lymphoma, particularly Hodgkin disease. In most patients, neurologic symptoms prompt medical attention before the cancer itself has been identified. The cancer is usually then found within months to a year after the onset of neurologic symptoms; however, occasionally it may elude detection for several years and in some instances is found only at autopsy.

Typically, the disorder begins with dizziness or vertigo, nausea, and vomiting followed rapidly by gait ataxia evolving rapidly over days to a few months to include incoordination in the arms, legs, and trunk; dysarthria is also often present, as is nystagmus associated with oscillopsia. Within a few months, the illness usually reaches its peak and then stabilizes. By this time, most patients cannot walk and many cannot sit unsupported. Handwriting is impossible, independent eating is difficult, and speech may be difficult to understand. Oscillopsia may prevent reading or even watching television. The neurologic signs are always bilateral and usually symmetric, although at times one side may be more affected than the other. In occasional patients, this asymmetry is quite prominent. Diplopia is an early symptom in many patients, although abnormalities of ocular muscles are often not detected by the examiner. Exceptions include those with abrupt onset and patients with a milder course so that the patient can walk, write, and be understood, albeit with some difficulty.

The signs and symptoms are frequently limited to those of cerebellar or cerebellar pathway dysfunction but, in as many as 50 percent of patients, other neurologic abnormalities, usually mild, may be found on careful examination, including sensorineural hearing loss, dysphagia, hyperreflexia with or without extensor plantar responses, extrapyramidal signs, peripheral neuropathy, and cognitive abnormalities including dementia. Studies using formal neuropsychologic testing have challenged the notion of cognitive dysfunction, finding that dementia is not common when testing is controlled for impaired motor and speech production.

LABORATORY EVALUATION

Early in the course of the disease, the brain MRI is usually normal (Fig. 27-2A). However, a reduced NAA/Cr ratio on MR spectroscopy of the cerebellar vermis may occur when routine MRI is normal. If patients are followed for months to a few years, diffuse cerebellar atrophy appears (Fig. 27-2B). Occasional patients have been reported in whom hyperintensity is found in the cerebral and cerebellar white matter on T2-weighted images. Rarely, transient contrast enhancement of the cerebellar folia may suggest leptomeningeal tumor along with associated edema, which may cause hydrocephalus.

In most patients who are studied early in the course of the disease, the CSF contains an increased number

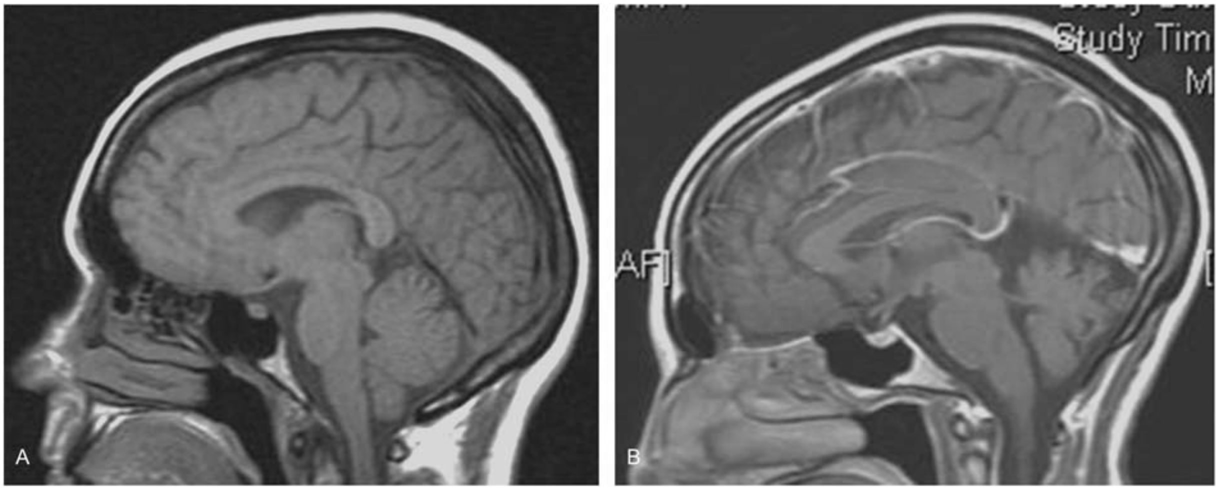

FIGURE 27-2 ■ *A*, Normal sagittal MRI of the brain. *B*, T1 contrast-enhanced sagittal MRI of the brain in a patient with paraneoplastic cerebellar degeneration. The cerebellum is atrophic, but the rest of the brain is normal.

of lymphocytes, slightly elevated protein level, and increased IgG index along with unique oligoclonal bands. The pleocytosis usually resolves with time. Some, but not all, patients with paraneoplastic cerebellar degeneration have autoantibodies in serum and CSF that react with Purkinje cells of the cerebellum and the causal tumor.

The antibody most frequently associated with pure cerebellar degeneration is against Yo (Table 27-5). This antibody recognizes a major protein antigen termed CDR2L, which is expressed in Purkinje cells of the cerebellum and in the patient's tumors. CDR2 was a previously considered antigenic target of these antibodies and may be recognized by the Yo antibodies when expressed in non-native detection systems. Yo antibodies show evidence of intrathecal synthesis from B cells that have crossed into the brain. In addition to the antibody response, cytotoxic T cells against CDR2 have also been described. Patients with breast cancer and Yo-antibody cerebellar degeneration also usually overexpress HER2.

A second autoantibody commonly found in patients with paraneoplastic cerebellar degeneration is the Tr antibody that occurs in patients with paraneoplastic cerebellar degeneration related to Hodgkin disease. The disorder often begins following the diagnosis of Hodgkin disease and sometimes when patients are in remission. The clinical presentation is generally less severe than in patients with Yo antibodies. The prognosis for successful treatment of the underlying tumor is good. Interestingly, and in alignment with this clinical improvement, the antibodies are now known to target the extracellular domain of the delta/notch-like epidermal growth factor-related receptor.

Hu antibodies usually associate with cerebellar degeneration as a part of a more widespread encephalomyelitis syndrome. In some patients, cerebellar symptoms outweigh other symptoms; in other patients, sensory neuronopathy is prominent so that it is difficult to discern the localisation or basis of the ataxia. As with the Yo antibody syndrome, symptoms may be sudden in onset and pathologic examination reveals substantial loss of Purkinje cells. Inflammatory infiltrates in Purkinje cells or the cerebellar dentate nucleus are often found in patients with the Hu antibody, perhaps because patients only survive for a short period of time.

Other less common antibodies include Ma, an antibody that recognizes both Ma1 and Ma2, which are antigens restricted to brain and testis. The paraneoplastic disorder usually is associated with encephalomyelitis, particularly brainstem and hypothalamic dysfunction, and is associated with a variety of tumors including those of breast and colon. The Ri antibody (discussed later in the section on opsoclonus) is also associated with paraneoplastic cerebellar degeneration, usually as part of the opsoclonus-myoclonus syndrome. CRMP5 (CV2) antibodies are directed against an antigen in some oligodendrocytes; the disorder has been associated with a number of neurologic problems including optic neuritis and paraneoplastic cerebellar degeneration. The most common tumor is thymoma, although some patients have SCLC and gynecologic malignancies. P/Q VGCC antibodies associated with LEMS and SCLC are also occasionally

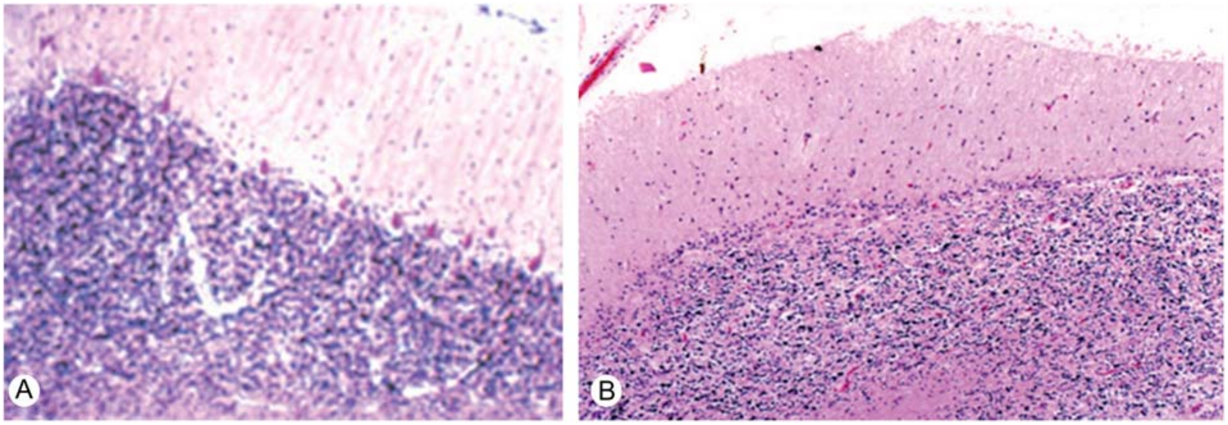

FIGURE 27-3 ■ Paraneoplastic cerebellar degeneration. *A*, Section of cerebellum of a patient who died of cancer without cerebellar symptoms. Multiple Purkinje cells are identified between the molecular *(top)* and granule cell *(bottom)* layers, both of which are normal (hematoxylin–eosin ×25). *B*, Section of cerebellum from a patient with autoantibody-positive paraneoplastic cerebellar degeneration. The molecular and granular cell layers are relatively normal, but Purkinje cells are absent, and there is a slight increase in Bergmann astroglia along with some inflammatory cells in the leptomeninges (hematoxylin–eosin ×25).

associated with paraneoplastic cerebellar degeneration. mGluR1 antibodies have been reported in patients with Hodgkin disease and paraneoplastic cerebellar degeneration. Also, patients have been reported with cerebellar ataxia as part of their CASPR2-antibody associated syndrome. A more recent description of vertigo, ataxia, and diplopia in conjunction with testicular seminomas has been associated with autoantibodies against kelch-like protein 11 (KLHL11). This, alongside CASPR2- and GAD-antibody ataxias, may be treatable forms of autoimmune ataxia. Zic4 antibodies have also been associated with cerebellar degeneration as well as encephalomyelitis in patients with SCLC, as have PCA2 and ANNA-3 antibodies. Other rarer antibodies include CARP VIII antibodies (usually with melanoma), proteasome in association with Yo antibodies (ovary and breast cancers), PKC gamma (NSCLC), Ca (no cancer yet identified), and as yet unnamed antibodies.

PATHOLOGY

In paraneoplastic forms of cerebellar ataxia, the CNS may appear grossly normal when examined at autopsy, but usually the cerebellum is atrophic, with abnormally widened sulci and small gyri. Microscopically, the hallmark of paraneoplastic cerebellar degeneration is severe, often complete, loss of the Purkinje cells of the cerebellar cortex (Fig. 27-3). Degenerating Purkinje cells may have swellings, termed torpedoes, along the course of their axons. Other pathologic features may include thinning of the molecular and granular layers of the cerebellar cortex, often without marked cell loss, and proliferation of astrocytes. The deep cerebellar nuclei are usually well preserved, although rarefied white matter may surround the nuclei, caused by the loss of Purkinje cell axons. Basket cells and tangential fibers are usually intact. Lymphocytic infiltrates, if present, are usually found in the leptomeninges around the cerebellum, in the dentate nucleus, and throughout the surrounding white matter; they are rare in the Purkinje cell layer.

In many patients, the disorder is noninflammatory, with pathologic changes restricted to the Purkinje cell layer of the cerebellum. However, pathologic changes outside the cerebellum do occur in some patients, including degeneration of the dorsal columns and pyramidal tracts of the spinal cord, degeneration of the basal ganglia (specifically the pallidum), loss of peripheral nerve fibers, and inflammatory infiltrates in the brainstem, spinal cord, and cerebral cortex.

The tumors associated with paraneoplastic cerebellar degeneration do not differ histologically from similar tumors unassociated with paraneoplastic symptoms except that the tumors are usually found to be infiltrated with lymphocytes and plasma cells. In many patients, the tumor, when identified, is still localized; metastases, if present, are usually found only in regional lymph nodes.

Diagnosis

The diagnosis depends on recognizing the characteristic clinical syndrome and excluding other cancer-associated causes of late-onset cerebellar dysfunction, such as parenchymal or leptomeningeal metastases, infections, and toxicity of therapies such as cytarabine (see Chapter 28). Causes unrelated to cancer, such as viral brainstem encephalitis or cerebellitis, demyelinating disease, Creutzfeldt–Jakob disease, infarction, hypothyroidism, and alcoholic and hereditary cerebellar degeneration, must also be excluded.

A disorder clinically identical to paraneoplastic cerebellar degeneration may occur without a cancer being identified. How often subacute cerebellar degeneration is nonparaneoplastic is uncertain, but it may be 50 percent or higher. In patients with rapidly developing cerebellar syndromes, the physician should suspect a paraneoplastic disorder, particularly when the CSF contains a lymphocytic pleocytosis. The detection of autoantibodies will identify the neurologic disorder as being paraneoplastic and suggest the likely location of the tumor, although these tumors may be very small and difficult to identify. If evaluation including total-body PET scanning fails to identify a tumor, repeated searches may be necessary. Exploratory laparotomy with salpingo-oophorectomy has been recommended in postmenopausal women with Yo antibodies and whose evaluation, including pelvic scans and mammograms, is negative. This approach has been used in several patients, and in all except one (in whom breast cancer was identified 4 months later) a tumor of the gynecologic tract was found; the tumor is sometimes apparent only microscopically.

Treatment

Reviews addressing the treatment of paraneoplastic cerebellar degeneration are available elsewhere. Overall, treatment is commonly unsuccessful, perhaps in part due to the death of Purkinje cells. The general treatment approach requires identifying and treating the causal tumor and then attempting immunosuppression. Immunosuppressive treatments have included high-dose corticosteroids. If the treatment is partially successful, consideration can be given to courses of intravenous immunoglobulin, cyclophosphamide, tacrolimus, rituximab, and mycophenolate.

Individual case reports indicate that treatment of the tumor and immunosuppression either stabilize or improve paraneoplastic cerebellar degeneration. In general, however, the Hu and Yo antibody patients rarely improve, whereas Tr or CRMP5 antibody disorders may have a better prognosis. Symptomatic improvement in the ataxia occurs in a few patients using clonazepam in daily doses varying from 0.5 to 1.5 mg. Buspirone may also give modest relief.

Opsoclonus-Myoclonus

Opsoclonus consists of involuntary, arrhythmic, multidirectional, conjugate saccades without an intersaccadic interval. Opsoclonus is often associated with diffuse or focal myoclonus as well as truncal titubation, with or without other cerebellar signs. Opsoclonus-myoclonus, also referred to as opsoclonus-myoclonus ataxia syndrome (OMAS), occurs primarily in children as a self-limited illness, probably the result of a viral infection affecting the brainstem. The disorder is paraneoplastic in about 40 percent of children. Although neuroblastoma is the common associated tumor, less than 2 percent of children with neuroblastoma have opsoclonus. However, given the known tendency of neuroblastoma to resolve spontaneously, some patients with OMAS without tumor may, in fact, have had a paraneoplastic form. These children are more likely to suffer from intrathoracic tumors with a benign pathology. Neuroblastoma prognosis is better in patients who have a paraneoplastic syndrome.

The age at peak incidence is 18 months, with more girls than boys affected. Neurologic signs precede identification of the tumor at least 50 percent of the time, making recognition of the neurologic syndrome an important clue to the presence of neuroblastoma. Ataxia, irritability, vomiting, and dementia may accompany opsoclonus-myoclonus.

A number of autoantibodies have been described in neuroblastoma-related OMAS. Affected children have a high incidence of antibodies that react with CNS antigens, but no particular antibody is pathognomonic for the syndrome. An autoantibody that binds the surface of cerebellar granule cells and is cytotoxic to neuroblastoma cell lines has been identified in pediatric patients with opsoclonus-myoclonus, with or without neuroblastoma. Some of the children had other antibodies that also reacted with cerebellar structures, including the Hu antibody. Elevated antibodies against the GluD2 receptor have been reported, as have elevated serum concentrations of Th2-chemokines.

Opsoclonus may respond to treatment with corticotropin (ACTH), plasma exchange, intravenous immunoglobulin, or rituximab and may improve after chemotherapy for the tumor. Multimodal therapy is better than corticotrophin alone. Unfortunately, many patients develop relapses and are left with significant cognitive deficits.

The disorder is less common in adults and is paraneoplastic in 15 to 20 percent of adults. Lung cancer is the most common cause, followed by ovarian teratoma. Neurologic symptoms usually precede the diagnosis of tumor and progress over several weeks, although more rapid or slower progression is observed in some instances. Opsoclonus is often associated with truncal ataxia, dysarthria, myoclonus, vertigo, and encephalopathy; some patients appear to have paraneoplastic cerebellar degeneration as well, and ophthalmoplegia has been reported. A mild CSF pleocytosis and a slightly elevated protein level are present in most patients. The results of neuroimaging are usually normal; in a few patients, an abnormality in the brainstem or cerebellum is detected by MRI. The Ri antibody is the most common associated known serology, typically occurring in women with breast cancer and other gynecologic tumors. This antibody identifies a protein called Nova, an RNA-binding protein that regulates aspects of synaptic proteins, including the glycine and $GABA_A$ receptors in the brainstem. Identifiable antibodies are usually not found in patients with opsoclonus and SCLC or ovarian teratomas.

Nonparaneoplastic causes of opsoclonus-myoclonus include viral infections, parainfectious syndromes, infection with human immunodeficiency virus, and toxic or metabolic encephalopathies. In many instances the cause is unknown. Immunosuppressive agents sometimes appear to be effective, although spontaneous remissions have also been described, making it difficult to interpret positive results. In the paraneoplastic form, the syndrome responds less well to immunotherapy unless the tumor is also treated.

Visual Loss

Paraneoplastic and nonparaneoplastic syndromes can cause visual loss by affecting either the retina or the optic nerve. They can affect photoreceptors (either rods, cones, or both) or can cause a retinal vasculitis. A paraneoplastic visual disorder can occur either as an isolated phenomenon or as part of a more widespread encephalomyelopathy or demyelinating process.

RETINOPATHY

Although all paraneoplastic visual disorders are rare, paraneoplastic retinal degeneration, also called cancer-associated retinopathy, is the most common. The two most common disorders are cancer-associated retinopathy and melanoma-associated retinopathy. The former disorder usually occurs in association with SCLC and gynecologic tumors. Typically, the visual symptoms, which include episodic visual obscurations, night blindness, light-induced glare, photosensitivity, and impaired color vision, precede the diagnosis of cancer. The symptoms progress to painless visual loss and may begin unilaterally before usually becoming bilateral. Visual testing demonstrates peripheral and ring scotomas along with loss of acuity. Fundus examination may reveal arteriolar narrowing and abnormal mottling of the retinal pigment epithelium; the electroretinogram is abnormal. The CSF is typically normal. Inflammatory cells are sometimes seen in the vitreous using slit-lamp examination. Pathologically, a loss of photoreceptors and ganglion cells with inflammatory infiltrates and macrophages is usually found. Other parts of the optic pathway are preserved, although a loss of myelin and lymphocytic infiltration of the optic nerve may occur. The melanoma-associated form is usually less severe, and generally occurs in patients already known to have melanoma; symptoms include night blindness, photopsias, and visual glare.

Several autoantibodies have been identified in patients with cancer-associated retinopathy, the most common of which is recoverin. Recoverin is a 23-kDa protein that modulates dark and light adaptation through calcium-dependent regulation of rhodopsin phosphorylation in photoreceptor cells. Several other autoantibodies may also occur in patients with paraneoplastic visual loss. Treatment of cancer-associated retinopathy is usually unsuccessful, despite immunosuppression and treatment of the cancer. A number of different antibodies have been detected in the serum of patients with melanoma-associated retinopathy and, like cancer-associated retinopathy, treatment is usually not effective.

OPTIC NEURITIS AND NEUROPATHY

Paraneoplastic optic neuropathy occurring in the absence of other neurologic symptoms is extremely uncommon. Patients with optic neuritis (some of whom also have retinitis) may harbor antibodies to collapsin response-mediator protein (CRMP5). These patients present with subacute visual loss; optic discs are swollen and visual field defects are typically present. Patients have a variety of other neurologic symptoms including cognitive changes, chorea, ataxia, sensory neuropathy, and myelopathy. The most common associated cancer is SCLC.

Far more commonly, outside of the context of multiple sclerosis, acute optic neuritis is a nonparaneoplastic phenomenon associated with antibodies against the extracellular domain of the astrocyte endfoot protein, AQP4.[13] Typically, patients with AQP4 antibodies present with severe and painful visual loss. Also, AQP4 antibodies often associate with other clinical features including a longitudinally extensive transverse myelitis (LETM) and an area postrema syndrome with hiccups and vomiting. The longitudinal and typically edematous imaging features are characteristic and are observed in both the optic nerve and the spinal cord. The natural history of these AQP4 antibody-mediated neuromyelitis optica spectrum-disorders (NMOSD) is a tendency to relapses which are the major cause of disability. The condition can affect a variety of ages, with a female preponderance. NMOSD is rarely a paraneoplastic condition.

In the acute phase, treatment with corticosteroids and plasma exchange are considered effective. For relapse prevention, there are data to support all of corticosteroids, azathioprine, mycophenolate mofetil, anti-CD20, and anti-CD19 drugs. In addition, and consistent with the complement fixing-dominant IgG1 subclass of AQP4 reactive autoantibodies, a C5 esterase inhibitor has shown efficacy in relapse reduction. Live cell-based assays, utilizing HEK cells which transiently express AQP4 are considered the gold standard for diagnosis.

Spinal Cord Syndromes

Paraneoplastic and nonparaneoplastic disorders may affect the spinal cord, either in isolation or as part of a more widespread encephalomyelitis. The below section will focus on disorders other than NMOSD.

MYELITIS

Paraneoplastic non-necrotizing myelitis occurs rarely as an isolated syndrome, and more commonly as a part of diffuse encephalomyelitis. Patients present with progressive weakness, sometimes with lower motor neuron signs including fasciculations, in association with sensory loss and autonomic dysfunction (e.g., incontinence and postural hypotension). The disorder may rarely be episodic or primarily involve posterior column function. Upper extremity findings often predominate owing to cervical cord involvement, and respiratory failure may occur. The differential diagnosis includes compressive or intrinsic spinal cord masses, other inflammatory or infectious myelopathies, and radiation injury. The CSF is typically inflammatory. Neuroimaging usually shows a normal spinal cord but, occasionally, expansion or hyperintensity of the spinal cord can be identified on T2-weighted MRI; rarely, contrast enhancement is present. No treatment is effective.

Pathologically, an intense inflammatory reaction with neuronal loss in the anterior and posterior horns is seen, with secondary nerve root degeneration and neurogenic muscle atrophy. Inflammation and degeneration of white matter tracts also can occur. A number of antibodies have been reported, including those which target CV2/CRMP5, amphiphysin, Hu, and Ri.

Subacute necrotizing myelopathy is a rare syndrome that occurs with lymphoma, leukemia, or most commonly lung cancers. Patients typically present with rapidly ascending flaccid paraplegia; back pain or radicular pain may herald the onset of neurologic dysfunction. The disease may ascend in the spinal cord, leading to respiratory failure. Inflammatory cells are usually present in the CSF. The MRI may be normal or show spinal cord swelling or contrast enhancement. The absence of an epidural mass or discrete intramedullary enhancement rules out metastatic myelopathy, which is much more common. Treatment is usually unsuccessful, although some patients respond to immunosuppression including corticosteroids. Pathologically, there is widespread necrosis involving all components of the spinal cord, but with some white matter predominance. Inflammatory infiltrates are not typical.

Motor neuron disease-like presentations may occasionally occur as a paraneoplastic syndrome. This can resemble amyotrophic lateral sclerosis with both upper and lower motor neuron dysfunction, or it may present as a progressive muscular atrophy mimic, with a pure lower motor neuron syndrome that is sometimes reversible and is associated with lymphoproliferative disorders. Subacute, nonreversible lower motor neuron syndromes have been reported in patients with Hu antibodies and SCLC. Primary lateral sclerosis, a pure upper motor neuron syndrome, is associated with solid tumors as well as with lymphoproliferative disorders. The clinical and pathologic characteristics differ little from nonparaneoplastic motor neuron disease except that the paraneoplastic disorders are often more rapid in onset and evolution, sometimes reverse spontaneously, and, at autopsy, may have more inflammatory cells than the nonparaneoplastic forms.

More recently, a group of patients with very similar optic nerve and spinal cord characteristics to NMOSD are recognized in association with antibodies to MOG. These patients are often younger than those with AQP4 antibodies, may have an associated encephalopathy, and around 50 percent have a monophasic disease course. However, relapsing disease is well recognized and necessitates individualized decisions about treatment duration. MOG antibodies are also only rarely a paraneoplastic association. In a manner akin to AQP4 antibody detection, and consistent with the concept of preferential native autoantigen targeting, MOG antibodies are most accurately detected with live cell-based assays.

STIFF-PERSON SYNDROME

Originally called the stiff-man syndrome, although it affects more women than men, this disorder is characterized by muscle stiffness and rigidity that are usually painful. The muscles involved almost always include the paraspinal and abdominal muscles and usually those of the lower extremities. In some instances, the illness is restricted to a single extremity ("stiff limb" syndrome). Sustained muscle contraction results in abnormal postures, such as an exaggerated lumbar lordosis. In addition to the chronic contractions, severe episodic muscle spasms may be precipitated by voluntary movements, unexpected environmental stimuli, and emotional upset. The arms are less commonly involved, and although stiffness of the neck and face can occur, it is rarely severe. On examination, the muscles feel hard and may be difficult to move passively. An unexpected external stimulus or a voluntary movement may precipitate an observable spasm. The electromyogram (EMG) is characterized by sustained continuous motor-unit activity that disappears during sleep and general anesthesia.

The nonparaneoplastic form of the disorder is associated with type 1 diabetes and antibodies to GAD. The paraneoplastic disorder is associated with antibodies against amphiphysin, GAD, Ri, and gephyrin. The common associated tumors include breast cancer, SCLC, Hodgkin disease, and colon cancer. More recently, the extracellular domain of the glycine α-1 subunit receptor has been shown to be a target of antibodies which associate with stiff person syndromes, especially the progressive encephalomyelitis with rigidity and myoclonus subtype.[14] Although injection of either GAD65 or amphiphysin antibodies into animals reproduces aspects of the clinical syndrome, the glycine receptor surface targeting antibodies are intuitively more likely to be causative than antibodies to the several intracellular targets.

Benzodiazepines and baclofen may relieve symptoms. Treatment of the tumor and immunosuppression with corticosteroids, intravenous immunoglobulin, or repeated plasmapheresis are sometimes effective.

Peripheral Nerve and Dorsal Root Ganglion Syndromes

Virtually any of the abnormalities that can affect the peripheral nervous system of patients without cancer can also occur as a paraneoplastic syndrome, including subacute sensory neuronopathy (dorsal root ganglionitis), sensory peripheral neuropathy, sensorimotor peripheral neuropathy (either axonal or demyelinating), autonomic neuropathy, paraproteinemic neuropathy, vasculitic neuropathy (presenting as mononeuritis multiplex), and a pure motor neuropathy or neuronopathy. The exact incidence of these disorders is not established. In tertiary centers seeing undiagnosed neuropathy patients, the incidence of paraneoplastic neuropathy is less than 10 percent.

Subacute sensory neuronopathy is the most common type of paraneoplastic peripheral neuropathy and is usually associated with SCLC. Symptoms typically begin before the cancer is identified with dysesthetic pain and numbness in the distal extremities or occasionally in the face or trunk. The symptoms may be asymmetric at onset, but progress over days to several weeks to involve all limbs, causing a severe sensory ataxia. All sensory modalities are affected, distinguishing this disorder from cisplatin neuropathy, in which pinprick and temperature sensation are typically spared. Pain is occasionally a prominent symptom. Muscle stretch reflexes are usually lost, but motor function is preserved. The CSF typically contains a mild lymphocytic pleocytosis, particularly when the sensory changes are associated with encephalomyelitis. On nerve conduction studies, sensory nerve action potentials are diminished or absent, and compound muscle action potentials are normal; EMG evidence of denervation is absent.

Pathologic changes may be limited to the dorsal root ganglia, with neuronal loss and lymphocytic inflammatory infiltrates (Fig. 27-4). Secondary changes seen on sural nerve biopsy are usually characterized by a substantial reduction in myelinated fiber density with a

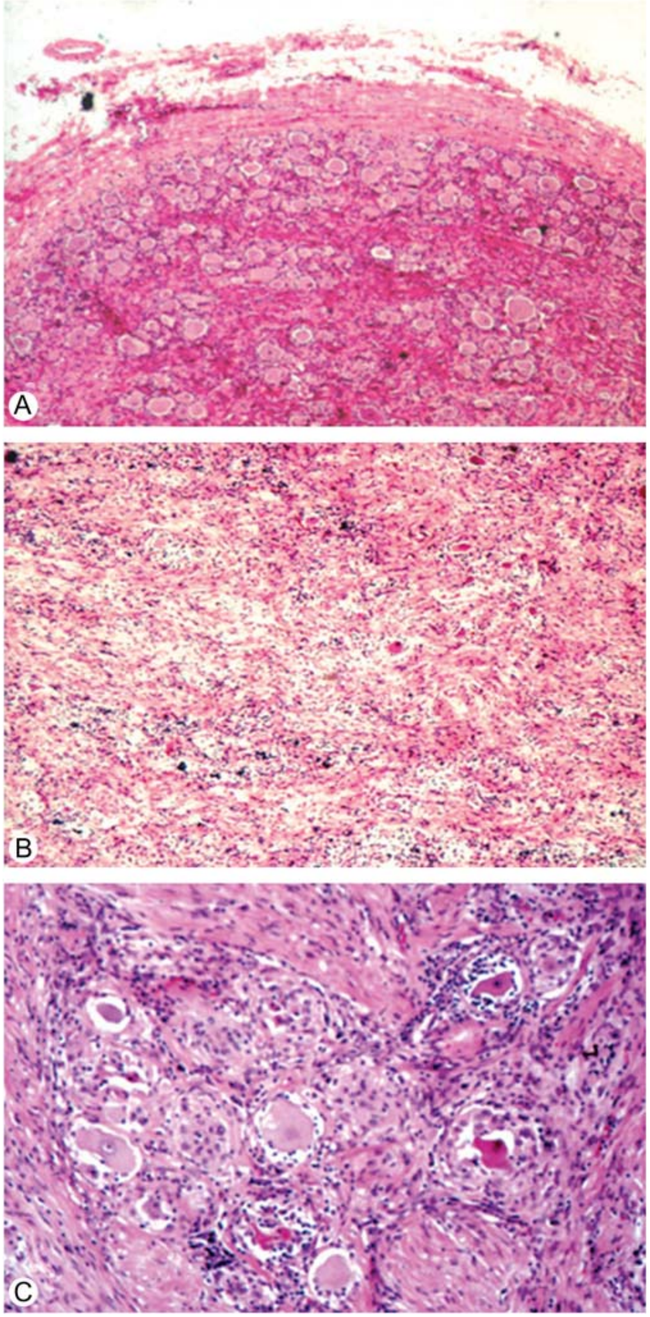

FIGURE 27-4 ■ Paraneoplastic sensory neuronopathy. *A*, Dorsal root ganglion obtained at autopsy from a patient without neurologic disease. *B*, Dorsal root ganglion obtained from a patient with paraneoplastic sensory neuronopathy and anti-Hu antibodies. Note that there are virtually no normal dorsal root ganglion neurons in the entire section. A few scattered inflammatory infiltrates are present (hematoxylin–eosin ×40). *C*, The dorsal root ganglion of another patient with Hu-antibody related subacute sensory neuronopathy. Degenerating neurons can be seen surrounded by inflammatory cells (hematoxylin–eosin ×40).

lesser reduction in small fibers; however, in those patients with severe painful neuropathy, small fibers are reduced more than myelinated fibers. In about 50 percent of patients, clinically inapparent pathologic changes are found in other regions of the nervous system. Treatment of the underlying tumor and removal of the autoantibody by plasmapheresis or immunosuppressive therapy may stabilize or sometimes improve symptoms, particularly when given early. Occasional patients have a mild and indolent sensory neuropathy.

Sensory neuronopathy can occur in previously healthy individuals or in those with a variety of underlying autoimmune conditions, including Sjögren syndrome. It can also be caused by heavy metal intoxication, including the platinum analogue chemotherapeutic agents. The disorder is paraneoplastic in only a minority of patients. At least two-thirds of patients with paraneoplastic sensory neuronopathy have SCLC as the cause. Criteria for distinguishing subacute sensory neuronopathy from other sensory neuropathies include the early development of sensory ataxia, an asymmetric distribution of sensory loss, sensory loss occurring in a nonlength-dependent manner beyond the distal lower extremities, and relatively normal motor but abnormal sensory conduction studies. Criteria for separating paraneoplastic subacute sensory neuropathy from other causes include an acute or subacute onset in four limbs, early pain, and its occurrence in men more than 60 years old. The presence of Hu antibodies is useful to confirm the paraneoplastic etiology, having a specificity of 99 percent and sensitivity of 82 percent. The more recently described antibodies against fibroblast growth factor receptor 3 may also be found in a few patients.

Subacute sensorimotor neuropathy is predominantly a distal symmetric polyneuropathy that is more marked in the lower than upper extremities and is characterized by weakness, stocking-and-glove sensory impairment to all modalities, and a loss of muscle stretch reflexes. Bulbar involvement is uncommon. Patients with mild sensory or sensorimotor neuropathy that evolve slowly over many months to years are unlikely to have carcinoma as the underlying cause. By contrast, patients with a subacute onset of a severe peripheral neuropathy leading to substantial paralysis and sensory loss are much more likely to have a paraneoplastic syndrome. A few patients with paraneoplastic sensorimotor neuropathy follow the remitting and relapsing course typical of chronic inflammatory demyelinating polyneuropathy; these patients may respond to corticosteroid therapy. Guillain–Barré syndrome, acute brachial neuritis, cauda equina syndrome, and dysfunction of individual nerves are occasionally paraneoplastic.

In most paraneoplastic sensorimotor neuropathies, the CSF is typically acellular with a normal or slightly elevated protein concentration. Nerve conduction studies are consistent with an axonal neuropathy, with low-amplitude or absent sensory nerve action potentials and normal or decreased motor nerve conduction velocities. A few patients have marked slowing of motor conduction velocities consistent with a demyelinating process. Pathologically, there is usually axonal degeneration; in a few patients, demyelination is prominent.

A relatively pure *paraneoplastic sensory neuropathy* (not neuronopathy) occurs with a variety of malignancies, but cannot be distinguished from other causes of sensory neuropathy. When no cause of a sensory neuropathy is identified, cancer is subsequently found as the etiology in approximately one-third of patients. The mean time to cancer diagnosis following the neurologic disorder is more than 2 years.

A more recent set of autoantibodies directed against molecules which are critical to the function of the paranode and node of Ranvier have been described, and termed the "nodo-paranodopathies."[15] Robustly identified antigens include neurofascin 186/155, Caspr1, and contactin-1, but their association with specific tumors is limited. Each antigen appears to associate with some recognizable, but not highly specific, clinical features. For example, patients with neurofascin 155 antibodies have a young age of onset, motor predominance, ataxia, and tremor, sometimes with additional CNS involvement. Contactin-1 antibodies are often detected in patients with an aggressive onset and/or motor predominance, and Caspr1 antibodies often are seen in patients with rapidly progressive neuropathies, sometimes with neuropathic pain. Many of these patients show a clear response to immunotherapies, and some of the autoantibodies already have demonstrated pathogenic characteristics.

Peripheral neuropathy due to microvasculitis is rare as a paraneoplastic syndrome and is found without obvious antibody involvement in patients with a variety of cancers. Vasculitic neuropathy can present either as a diffuse polyneuropathy or as mononeuritis multiplex. It can involve both peripheral and cranial nerves. The importance of making a diagnosis, which may require nerve biopsy, is that the condition may respond to corticosteroid treatment.

Peripheral neuropathy may be associated with multiple myeloma and Waldenström macroglobulinemia. With the rare osteosclerotic form of myeloma, peripheral neuropathy is present in about 50 percent of patients. Successful treatment of the myeloma often leads to amelioration of the neurologic symptoms. Amyloidosis associated with myeloma can also cause a peripheral neuropathy that responds poorly to treatment. Options for therapy include both tumor treatment and immunosuppression. Rituximab is effective in treating some neuropathies associated with IgM antibodies (Fig. 27-5).

AUTONOMIC NEUROPATHY

Paraneoplastic autonomic neuropathy is a rare syndrome that occurs alone or along with a sensory neuronopathy. Usually associated with SCLC, it may occur with other cancers and may present before or after the cancer is diagnosed. Patients present with the subacute onset of postural hypotension, pupillary abnormalities, a neurogenic bladder, or some combination of these signs. Severe constipation may be the only symptom of this paraneoplastic disorder. The syndrome is generally progressive but may stabilize or improve with treatment of the underlying tumor. When autonomic neuropathy occurs with lung cancer, it is usually part of the Hu antibody syndrome. Autonomic neuropathy also occurs with an antibody against the ganglionic acetylcholine receptor (nAChR), often without an underlying tumor. Immunization with the protein produces an autonomic neuropathy, as does passive transfer of antibodies, indicating a B cell-mediated disease. Immunosuppression including agents such as plasma exchange, rituximab, and cyclophosphamide can prove effective.

NEUROMUSCULAR JUNCTION SYNDROMES

Paraneoplastic disorders of the neuromuscular junction include LEMS and myasthenia gravis. These disorders have a common underlying mechanism in that they are caused by antibodies against ion channels and, whether paraneoplastic or not, they often respond to immunologic treatment.

LEMS is characterized by progressive proximal weakness and fatigability, but, unlike myasthenia gravis, oculobulbar symptoms are usually not severe.

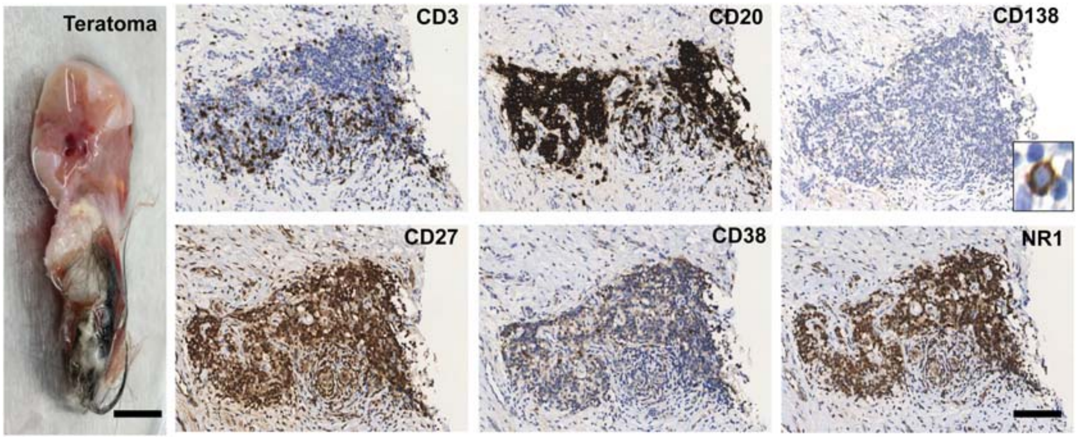

FIGURE 27-5 ■ The germinal centers in ovarian teratomas (scale bar in far left panel, 0.2 cm) of patients with NMDAR-antibodies. T cells (CD3) oppose B cells (CD20) with some plasma cells (CD138) around the rim of the lymphoid aggregates. Additional lymphocyte markers include CD27 and CD38. The dominant antigen of the patient's autoantibodies, the NR1 subunit of the *N*-methyl-D-aspartate receptor, is densely expressed in the tumor (scale bar in far right panel, 100 μm). (From Makuch M, et al: *N*-methyl-D-aspartate receptor antibody production from germinal center reactions: therapeutic implications. Ann Neurol 83:553, 2018, with permission.)

Respiratory weakness may occur. Power initially increases with effort, so that reported weakness may seem out of proportion to the examiner's findings; however, with continued effort, weakness returns. Muscle stretch reflexes, especially those in the legs, are diminished or absent but may reappear after exercise. Cholinergic dysautonomia occurs in more than 50 percent of patients, causing dry mouth and impotence. Characteristic abnormalities are found on electrophysiologic testing, including very small compound muscle action potentials that may increase to normal after brief exercise. Repetitive stimulation causes a decrement of the compound muscle action potentials at low rates of stimulation and an increment at high rates of stimulation. About 60 percent of patients with LEMS have SCLC; a few have other cancers. Some of the 40 percent who do not have cancer may have evidence of other autoimmune diseases.

The disorder results from reduced release of ACh at presynaptic nerve terminals. Antibodies that react with the P/Q-type VGCC are found in patients with or without paraneoplastic syndromes. The same P/Q-type VGCC antibodies are found in SCLC; the richest source of these channels is the cerebellum, perhaps explaining the occasional relationship of paraneoplastic cerebellar degeneration and LEMS.

LEMS is a classic autoimmune disease in that binding of circulating IgG antibodies to the VGCC reproduces the electrophysiologic abnormalities in animals; removal of IgG antibodies from humans with the disorder improves neurologic function. Accordingly, LEMS can be treated either by immunosuppression or by treatment of the underlying cancer when present. 3,4-Diaminopyridine (3,4-DAP) may improve the muscle weakness but can be difficult to obtain. Patients with SCLC-associated LEMS have a better prognosis than patients with SCLC who do not develop a paraneoplastic disorder. SOX1 antibodies are reported in 64 percent of patients with paraneoplastic LEMS but are not found in nonparaneoplastic LEMS.

Myasthenia gravis usually affects ocular, bulbar, and respiratory muscles, often sparing the extremities. In contrast to LEMS, patients grow weaker with exercise and improve with rest; repetitive stimulation decreases the compound muscle action potentials on EMG. Myasthenia gravis is usually not associated with cancer, but about 15 percent of patients have thymoma. The disorder is caused by antibodies against the ACh receptor at the neuromuscular junction. Patients with thymoma-associated myasthenia are more likely to also have other antibodies against muscle proteins such as ryanodine receptors. Myasthenia gravis usually responds to immunosuppression, acetylcholinesterase inhibitors, and thymectomy. Thymectomy is also proven to be beneficial in patients with nonthymomatous myasthenia gravis. Patients with myasthenia gravis can also have antibodies against another protein expressed at the neuromuscular junction, muscle-specific kinase (MuSK). MuSK antibody patients have some unique associated features including prominent bulbar involvement, early tongue atrophy and, importantly, a good response to rituximab.

PERIPHERAL NERVE HYPEREXCITABILITY (NEUROMYOTONIA)

Several disorders characterized by hyperexcitability at the terminal arborizations of peripheral nerves occur in patients with paraneoplastic syndromes, including neuromyotonia, the cramp-fasciculation syndrome, and Morvan syndrome.

Neuromyotonia occurs when single motor unit potentials fire spontaneously at 150 to 300 Hz, leading to chronic contraction of muscles that can be either focal or generalized. In its mildest form it is called myokymia (repetitive and recurrent firing of a motor unit potential at 2 to 60 Hz), clinically visible as undulating muscle twitching. The disorder is sometimes associated with neuropathic pain and autonomic dysfunction, especially hyperhidrosis. Patients may also demonstrate pseudomyotonia (failure of muscles to relax after contraction) and intestinal pseudo-obstruction. Some patients develop CNS symptoms of memory loss, hallucinations, insomnia, and changes in mood (Morvan syndrome). When these disorders are paraneoplastic, in around 50 percent of Morvan cases and 10 to 20 percent of isolated neuromyotonia cases, thymoma is the most common cause, but SCLC and Hodgkin disease have also been reported. There are several other underlying causes, including nerve damage associated with radiation therapy, snake bites, ion channel mutations, and inherited neuropathies. However, the disorder is often autoimmune and associated with antibodies against CASPR2, and, sometimes, against LGI1 or contactin-2.

The serum creatine kinase level is elevated in about one-half of patients. The diagnosis can be made electrophysiologically when needle EMG reveals spontaneous firing of single or multiple motor units at a rate of 150 to 300 Hz. These units fire at irregular intervals and may persist during sleep, general anesthesia, and even when peripheral nerves are blocked at proximal sites. Symptoms are relieved by blocking the neuromuscular junction, suggesting that the action potentials arise from terminal arborizations of the motor nerve.

CASPR2 and LGI1/contactin-2 antibodies have been shown to bind to neurons in areas of brain likely to cause the CNS symptoms. The definitive treatment is immunosuppression with corticosteroids, plasma exchange, or intravenous immunoglobulin. Many patients with mild forms of neuromyotonia respond to sodium channel blockers such as lamotrigine and phenytoin.

Muscle Syndromes

Polymyositis and dermatomyositis are common inflammatory autoimmune muscle diseases. Only a minority of patients suffering from these disorders have an underlying malignancy as the cause, particularly in older patients. Dermatomyositis with typical cutaneous changes is more likely than polymyositis to be paraneoplastic. Females and males are affected in approximately equal numbers. Symptoms of muscle weakness generally precede identification of the cancer, which may be at any site; breast, lung, ovarian, and gastric malignancies are the most common. Hodgkin disease and prostate and colon cancer have also been reported.

The clinical and laboratory findings in dermatomyositis and polymyositis associated with malignancy resemble those in the idiopathic disease, although cancer patients often have more striking abnormalities on muscle biopsy specimens. Patients characteristically present with proximal muscle weakness, elevated levels of serum creatine kinase, and EMG evidence suggesting a myopathic process. A muscle biopsy specimen showing an inflammatory myopathy confirms the diagnosis. Although laboratory findings do not distinguish paraneoplastic from nonparaneoplastic forms, the presence of the p155 antibody is more common in patients with cancer, whereas antisynthetase antibodies suggest an etiology not related to cancer. In fact, a range of autoantibodies has been described in various forms of myositis, perhaps most notably against HMG CoA reductase, the target of statin medications. Normal serum creatine kinase levels are occasionally found even in patients with profound muscle weakness, with or without malignancy; abnormal levels indicate a poor prognosis for the muscle disease. Weakness of respiratory and pharyngeal muscles may be life-threatening. The prognosis is not as good for the paraneoplastic disorder as it is for nonparaneoplastic forms. Corticosteroids, cyclosporine, and other immunosuppressants have been used successfully. High-dose intravenous immunoglobulin therapy is sometimes helpful in patients unresponsive to other forms of immunosuppression.

A necrotizing myopathy, with or without marked inflammation, has also been reported in patients with cancer, as has inclusion-body myositis. The necrotizing myopathy has been reported to respond to intravenous immunoglobulin, sometimes in spite of tumor progression. Corticosteroids, cyclosporine, and other immunosuppressants have also been used successfully.

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CHAPTER

28

Neurologic Complications of Chemotherapy and Radiation Therapy

THOMAS J. KALEY ■ LISA M. DEANGELIS

CHEMOTHERAPY
  Antimetabolites
    Fludarabine
    Methotrexate
    Cytarabine (Cytosine Arabinoside)
    Nelarabine
    Gemcitabine
  Mictrotubule Agents
    Ixabepilone
    Taxanes
    Vincristine
  DNA-Damaging Drugs
    Alkylating Agents
    Platinums
  Monoclonal Antibodies
    Bevacizumab
    Rituximab
  Small-Molecule Inhibitors
    Bortezomib and Carfilzomib
    Selumetinib
  Retinoids
  Immunotherapy
    Checkpoint Inhibitors
    Chimeric Antigen Receptor T-Cell Therapies
  Intrathecal Chemotherapy
RADIATION THERAPY
  Primary Neurologic Damage
    Brain
    Spinal Cord
    Cranial Nerves
    Peripheral Nerves
  Secondary Neurologic Involvement
    Radiogenic Tumors
    Vascular Abnormalities

Chemotherapy and radiation therapy (RT) are two of the major modalities used to treat cancer. Their goal is to kill or inactivate enough cancer cells that the body's own defenses can control the disease without unacceptable damage to normal tissue. Unfortunately, both RT and chemotherapy are relatively nonspecific and depend on their ability to do more damage to rapidly dividing cancer cells. The therapeutic/toxic ratio is often low; even in highly sensitive tumors such as acute lymphoblastic leukemia, Hodgkin disease, and germ cell tumors, for which the cure rate is high, many patients suffer serious side effects of therapy, either immediately or months to years later.

The nervous system may be expected to be relatively insensitive to the side effects of cancer therapy. It is protected from exposure to many chemotherapeutic agents by the blood–brain, blood–cerebrospinal fluid (CSF), and blood–nerve barriers. Furthermore, most neurons do not reproduce, and glia reproduce only slowly, thus affording protection against agents that are directed against dividing cells. Nevertheless, nervous system toxicity is common, second only to myelosuppression as a reason for limiting the dose of chemotherapy, and often is dose limiting for RT as well. Some newer therapies, especially targeted therapies (i.e., *ALK* inhibitors) are specifically designed to penetrate the central nervous system (CNS) to treat brain metastases; these agents could carry a greater risk of causing neurotoxicity. The purpose of this chapter is to describe the side effects of these therapeutic modalities on the central and peripheral nervous systems (PNS). The emphasis is on chemotherapeutic agents and radiotherapeutic approaches that are used widely in clinical practice, with particular attention to newer agents and especially the novel immunotherapies that have rapidly transformed the oncology landscape.

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TABLE 28-1 ■ Neurotoxicity of Chemotherapeutic Agents in Humans

		Neurotoxicity*		
Agents	**Drug**	**PNS**	**CNS**[†]	**Muscle**
Antimetabolites	5-Azacitidine	+	+	?+
	5-Fluorouracil	–	++	–
	Capecitabine	?+	+	–
	Cladribine	–	+	–
	Cytarabine	+	+	–
	Fludarabine	–	++	–
	Gemcitabine	?+	?+	+
	Methotrexate	–	++	–
	Nelarabine	++	+	–
	Pemetrexed	+	–	–
	Pentostatin	+	+	–
Alkylating agents	Carmustine (BCNU)	–	+	–
	Chlorambucil	–	?+	–
	Cyclophosphamide	–	?+	–
	Ifosfamide	–	++	–
	Lomustine (CCNU)	–	+	–
	Temozolomide	–	+	–
	Thiotepa	–	+	–
Platinums	Carboplatin	+	–	–
	Cisplatin	++	++	–
	Oxaliplatin	++	–	–
Taxanes	Cabazitaxel	++	–	+
	Docetaxel	+	–	+
	Nab-paclitaxel	++	–	+
	Paclitaxel	++	–	+
Vinca alkaloids	Vinblastine	+	–	–
	Vincristine	++	+	?+
	Vinorelbine	+	–	–
Podophyllotoxins	Etoposide (VP-16)	?+	?+	–
	Teniposide (VM-26)	?+	?+	–
Monoclonal antibodies	Bevacizumab	–	+	–
	Rituximab	–	+	–
Small-molecule inhibitors	Bortezomib	++	–	–
	Carfilzomib	+	+	–
	Gefitinib	–	+	–
	Imatinib	–	+	–
	Selumetinib	–	+	+
	Sorafenib	++	+	–
	Sunitinib	–	++	–
	Tipifarnib	++	+	–
	Vemurafenib	–	+	–
Other biologics	Cyclosporine	+	+	+
	Interferons	+	++	–
	Interleukins	–	++	–
	Lenalidomide	+	–	–
	Mycophenolate mofetil	+	+	–
	Tacrolimus	–	+	–
	Thalidomide	++	–	–
Miscellaneous	Dexamethasone	–	++	++
	DTIC (Dacarbazine)	–	?+	–
	Hexamethylmelamine	+	+	–
	Ixabepilone	++	–	–
	L-Asparaginase	–	+	–
	Procarbazine	+	+	–
	Retinoids	+	++	–
	Suramin	++	+	–
	Tamoxifen	–	+	–
	Immunotherapies (checkpoint inhibitors and CAR T cells)	+	+	+

*?+, questionable; +, rare; ++, common; –, none; CNS, central nervous system; PNS, peripheral nervous system.

[†] CNS and cranial nerves.

CHEMOTHERAPY

Table 28-1 classifies the major chemotherapeutic agents that have been reported to cause central nervous system (CNS) or PNS toxicity. Table 28-2 lists the neurotoxic signs caused by agents commonly used in cancer patients.[1]

TABLE 28-2 ■ Neurotoxic Signs Caused by Agents Commonly Used in Cancer Patients

Acute Encephalopathy (Delirium)	5-Azacytidine, 5-fluorouracil, asparaginase, bevacizumab, capecitabine, CAR T cells, carmustine, checkpoint inhibitors, cisplatin, cladribine, corticosteroids, cyclophosphamide, cyclosporin A, cytarabine, dacarbazine, docetaxel, etoposide (HD), fludarabine, gemcitabine, hydroxyurea, ifosfamide, imatinib, interferons, interleukins 1 and 2, methotrexate (HD, IV, IT), nelarabine, nitrosoureas (HD or arterial), paclitaxel, pentostatin, procarbazine, tacrolimus, tamoxifen, thalidomide, thiotepa (HD), tipifarnib, vincristine
Seizures	5-Fluorouracil, amifostine, asparaginase, bevacizumab, busulfan (HD), CAR T -cells, carmustine, cisplatin, corticosteroids, cyclophosphamide (HD), cyclosporin A, cytarabine, dacarbazine, docetaxel, erythropoietin, etanercept, etoposide (HD), fludarabine (HD), gemcitabine, hydroxyurea, ifosfamide, interferon, interleukin-2, letrozole, leuprolide, methotrexate, nelarabine, octreotide, paclitaxel, pentostatin (HD), temozolomide, teniposide, thalidomide, topotecan (IT), vincristine
Headaches Without Meningitis	5-Fluorouracil, anastrozole, asparaginase, CAR T cells, carmustine, capecitabine, cetuximab, cisplatin, cladribine, corticosteroids, cytarabine, erlotinib, estramustine, etoposide, fludarabine, gefitinib, gemtuzamab, hydroxyurea, ibritumomab, imatinib, interferons, interleukins, isotretinoin, ixabepilone, letrozole, leuprolide, methotrexate, nelarabine, panitumumab, procarbazine, retinoic acid, rituximab (IV and IT), sorafenib, sunitinib, tamoxifen, temozolomide, thalidomide, thiotepa, topotecan, traztusumab, vemurafenib, vincristine
Visual Loss	5-Fluorouracil, bevacizumab, carboplatin, carmustine, cisplatin, cytarabine, etanercept, etoposide, fludarabine, interferon, interleukin, ipilimumab, isotretinoin, methotrexate, nitrosoureas (IA), oxaliplatin, paclitaxel, pentostatin, tamoxifen, vincristine
Chronic Encephalopathy (Dementia)	5-Fluorouracil, carmofur, carmustine, cisplatin, cytarabine, dacarbazine, fludarabine, ifosfamide, interferon-alpha, methotrexate, rituximab (IT), topotecan (IT)
Peripheral Neuropathy	5-Azacitidine, 5-fluorouracil, bortezomib, cabazitaxel, capecitabine, carboplatin, carfilzomib, checkpoint inhibitors, cisplatin, cladribine, cytarabine, docetaxel, etoposide, fludarabine, gemcitabine, ifosfamide, interferon, ipilimumab, ixabepilone, lenalidomide, nab-paclitaxel, nelarabine, oxaliplatin, paclitaxel, pemetrexed, pentostatin, procarbazine, sorafenib, sunitinib, teniposide, thalidomide, tipifarnib, vinca alkaloids
Cerebellar Dysfunction (Ataxia)	5-Fluorouracil, cyclosporin A, cytarabine, nelarabine, procarbazine, vinblastine, vincristine
Myelopathy (Intrathecal Drugs)	Cytarabine, methotrexate, thiotepa
Aseptic Meningitis	Checkpoint inhibitors, cytarabine (IT), IVIg, methotrexate (IT), monoclonal antibodies, rituximab (IT), thiotepa (IT), topotecan (IT)

Ara-C, Cytosine arabinoside or cytarabine; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; HD, high-dose; IT, intrathecal; IV, intravenous; IVIg, intravenous γ-globulin; NSAIDs, nonsteroidal anti-inflammatory drugs; OKT-3, orthoclone; TNF, tumor necrosis factor.

Antimetabolites

FLUDARABINE

Fludarabine (2-fluoroadenosine arabinoside) is active against a variety of lymphoproliferative neoplasms. It is highly immunosuppressive and has been associated with the development of progressive multifocal leukoencephalopathy (PML) in some patients. In addition, fludarabine can cause delayed neurotoxicity leading to a severe encephalopathy and occasionally cortical blindness. Older patients and those receiving higher doses of the drug are at greater risk.

METHOTREXATE

Methotrexate causes both acute and delayed neurotoxicity. The side effects associated with intrathecal administration are listed in the section on Intrathecal Chemotherapy.

A stroke-like syndrome affecting adults or children occasionally follows systemic high-dose methotrexate infusion. The disorder usually follows the second or third treatment by 5 or 6 days and is characterized by alternating hemiparesis associated with aphasia and sometimes encephalopathy or coma. Unequivocal seizure activity is rare, and the electroencephalogram

(EEG) typically is slow. Magnetic resonance imaging (MRI) displays foci of hyperintensity on fluid-attenuated inversion recovery (FLAIR) sequences and diffusion-weighted imaging displays well-delineated hyperintense areas affecting the deep white matter but not conforming to a vascular territory. Apparent diffusion coefficient (ADC) maps demonstrate decreased signal intensity in a corresponding distribution, suggesting restricted diffusion, similar to an acute vascular event. Patients generally recover spontaneously in 48 to 72 hours with complete or partial resolution of the imaging abnormalities. Recurrences are rare with subsequent treatments. The pathogenesis is unknown.

Leukoencephalopathy may appear months to years following therapy, beginning insidiously or abruptly with personality changes and learning disability. The disorder generally follows repeated doses of intravenous high-dose methotrexate or intrathecal methotrexate, but it may occur after standard doses as well. Although the syndrome can be caused by methotrexate alone, it is enhanced by brain RT and the combination of systemic and intrathecal drug. The sequence of modalities is probably also important. When methotrexate is administered concurrently with or follows cranial RT, the synergy is particularly toxic. The clinical course varies. Patients may recover slowly over weeks or months, their symptoms may stabilize with a mild to moderate dementia, or relentless progression may occur, with spastic hemiparesis or quadriparesis, severe dementia, and coma, ending in death. Seizures can occur, usually late in the course. The MRI reveals cerebral atrophy, bilateral and diffuse periventricular white matter hyperintensity on T2-weighted or FLAIR sequences (Fig. 28-1), ventricular dilatation, and, sometimes, cortical calcifications. Similar findings may occasionally be seen in asymptomatic patients who have received methotrexate. Focal enhancement may be present in the early stages, but does not persist. Neurologic signs are usually preceded by radiographic white matter changes on MRI, and identical radiographic findings may be seen in patients years after prophylactic treatment with intrathecal or intravenous methotrexate, even in the absence of RT. No effective treatment exists.

Cytarabine (Cytosine Arabinoside)

Intravenous high-dose cytarabine (ara-C; 3 g/m^2 per 12 hours for 8 to 12 doses) may cause central or peripheral neurologic disorders. Cerebellar dysfunction occurs most frequently in older patients and in those with pre-existing renal dysfunction, usually at a cumulative dose ≥ 36 g/m^2; however, it has been reported after a single dose of 3 g/m^2. Patients develop dysarthria, nystagmus, and appendicular and gait ataxia. Confusion, lethargy, and somnolence may also occur. With cessation of the drug, complete resolution of symptoms and signs generally occurs within 2 weeks, but some have persistent deficits.

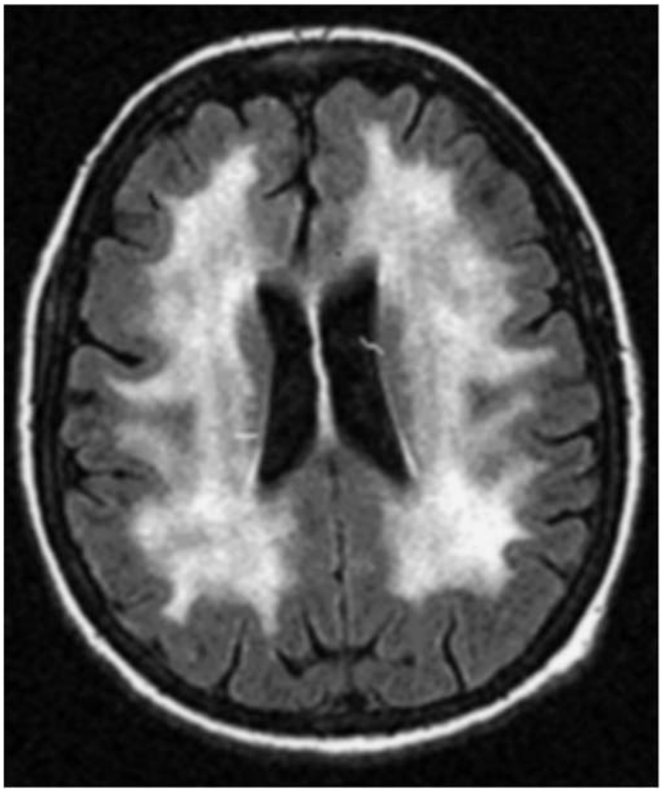

FIGURE 28-1 ■ Treatment-induced leukoencephalopathy. Fluid-attenuated inversion recovery magnetic resonance imaging of the brain demonstrates diffuse periventricular white matter hyperintensity following treatment with methotrexate and whole-brain radiotherapy.

Peripheral neuropathy, axonal or demyelinating or both, is a rare complication of ara-C. Other reported toxicities include seizures, intracranial hypertension, reversible ocular toxicity (blurred vision, photophobia, burning eye pain, and blindness), bulbar and pseudobulbar palsy, Horner syndrome, the "painful legs, moving toes" syndrome, brachial plexopathy, reversible bilateral lateral rectus palsies, and acute aseptic meningitis (after intravenous injection). There is no treatment for any of the neurotoxic effects of ara-C but many patients recover spontaneously.

NELARABINE

Nelarabine is a purine analogue that is used in the treatment of T-cell acute lymphoblastic leukemia. Motor and/or sensory peripheral neuropathy occurs in approximately 20 percent of patients. Central neurotoxicity most frequently includes somnolence and fatigue around 1 week after drug administration. Other symptoms include headache, seizures, ataxia, tremor, amnesia, and paraplegia has also been reported. The deficits may not be reversible and so drug discontinuation is recommended.

GEMCITABINE

Gemcitabine is a deoxycytidine analogue. Sensory neuropathy occurs in approximately 10 percent of patients, and autonomic neuropathy has also been reported. Gemcitabine can also cause an acute myositis, which may be multifocal. Patients may present with painful symmetric weakness of the proximal muscles, with elevation of muscle enzymes in the blood. Symptoms resolve rapidly with discontinuation of the drug and with corticosteroids, and patients often do well with rechallenge. Gemcitabine can also cause a focal myositis hours to days after administration, in a field previously irradiated months or even years earlier, known as radiation recall. Many other agents have also been associated with radiation recall, including capecitabine and docetaxel.

Mictrotubule Agents

IXABEPILONE

Ixabepilone is an epothilone that stabilizes microtubules and induces apoptosis. Neuropathy is the most common neurotoxicity, occurring in more than 60 percent. It is predominantly sensory, but a mild motor neuropathy may occur infrequently. The sensory neuropathy is generally mild to moderate and improves with drug discontinuation, typically within 1 to 2 months. Alternatively, dose reduction can be employed if the severity is no worse than grade 2 by National Cancer Institute common toxicity criteria (NCI CTC), and stopped if it reaches grade 3. Less common neurologic side effects include headache and dizziness.

TAXANES

Paclitaxel and Docetaxel

Approximately 60 percent of patients receiving paclitaxel (Taxol) at $\leq 250\,\text{mg/m}^2$ dose develop paresthesias of the hands and feet that do not usually progress and may resolve despite continued therapy. The neuropathy is predominantly sensory and affects all modalities. Paclitaxel causes axonal damage, with secondary demyelination, probably reflecting damage to the cell body. A few patients also develop proximal muscle weakness that resolves; it is usually associated with peripheral neuropathy. Acute arthralgia and myalgia of the legs that curtail activity (and are sometimes mistaken for neuropathy) may occur 2 to 3 days after a course of paclitaxel. Encephalopathy and seizures may occur, but are rare. Docetaxel causes the same type of sensory neuropathy as paclitaxel but is less neurotoxic. Paclitaxel or docetaxel neuropathy is enhanced by prior or subsequent neurotoxic chemotherapy, particularly cisplatin or vinorelbine. To date there are insufficient human data to support any neuroprotective agents against taxane-induced (or any chemotherapy-induced) peripheral neuropathy.

Nab-paclitaxel

Nab-paclitaxel, an albumin-bound formulation of paclitaxel, has a higher incidence of grade 3 sensory neuropathy compared to standard paclitaxel. Patients may improve with discontinuation, and the drug may be rechallenged at a reduced dose.

Cabazitaxel

Cabazitaxel is a semisynthetic taxane that can be effective in docetaxel- and paclitaxel-resistant tumors. Peripheral neuropathy can occur but is rarely severe.

VINCRISTINE

Vincristine affects primarily the peripheral nerves but can also be toxic to the CNS, cranial nerves, and autonomic nervous system (Table 28-3). Vinorelbine and vinblastine are much less neurotoxic. A dose-limiting sensorimotor neuropathy appears in virtually all patients. The earliest complaint is tingling and paresthesias of the fingertips and later of the toes. Fine movements of the fingers and toes are often

TABLE 28-3 ■ The Spectrum of Vincristine Neurotoxicity

Toxic Effect	Subacute (1 day–2 weeks)	Intermediate (1–4 weeks)	Chronic (>3 weeks)
Peripheral neuropathy	Depressed Achilles reflex (universal)	Other tendon reflexes depressed, paresthesias	Sensory loss, weakness, "foot drop" gait
Myopathy?	Muscle pain, tenderness, (especially quadriceps); jaw pain	–	–
Autonomic neuropathy	Ileus with cramping abdominal pain	Constipation, urinary hesitancy, impotence, orthostatic hypotension	–
Cranial neuropathy (uncommon)	–	–	Optic atrophy; ptosis; sixth, seventh, and eighth cranial nerve dysfunction; hoarseness; dysphagia
"Central" toxicity	–	Seizure, SIADH	–

Modified from DeAngelis LM, Posner JB: Neurologic Complications of Cancer. 2nd Ed, Oxford University Press, New York, 2009.
SIADH, syndrome of inappropriate antidiuretic hormone secretion.

impaired. Muscle cramps, usually diurnal, affect arms and legs and may be the first symptom of neurotoxicity. Weakness, especially of the extensors of the feet and hands, is frequent. Foot drop is either unilateral or bilateral; unilateral foot drop is more common in patients who have lost weight and habitually sit with crossed legs, causing peroneal nerve compression. The weakness is usually tolerable, but rarely patients may become bedbound or quadriparetic, particularly if there is a pre-existing neuropathy. The sensory symptoms, weakness, and lost reflexes are reversible, but may require months to improve after the medication is stopped. Neurophysiologic studies show an axonal neuropathy.

Vincristine occasionally causes *focal neuropathies* of peripheral or cranial nerves.[1] The most common is oculomotor nerve involvement with ptosis. Less frequent is ophthalmoplegia with diplopia. The recurrent laryngeal nerve, facial nerve, acoustic nerve, and optic nerve are also affected occasionally. These various neuropathies may be bilateral or unilateral. Night blindness due to retinal damage has also been reported.

Autonomic neuropathy, characterized by colicky abdominal pain and constipation, occurs in almost all patients. Rarely, paralytic ileus develops and may be fatal. Prevention of constipation is essential, and all patients should receive a prophylactic bowel regimen. Other manifestations of autonomic dysfunction include bladder atony, impotence, and postural hypotension.

CNS toxicity may result from hyponatremia due to inappropriate secretion of antidiuretic hormone (SIADH). Encephalopathy and focal or generalized seizures not associated with SIADH have also been reported. Cortical blindness and other CNS signs, including athetosis, ataxia, and parkinsonian-like symptoms, usually reverse after treatment is discontinued.

DNA-Damaging Drugs

ALKYLATING AGENTS

Ifosfamide

High-dose ifosfamide has been associated with a reversible encephalopathy of varying severity, which is a dose-limiting adverse effect. The most common manifestations include confusion, stupor, and mutism, rarely evolving into coma; less common features include seizures, hallucinations, personality changes, blurred vision, extrapyramidal symptoms, cerebellar symptoms, and urinary incontinence. EEG abnormalities are found in 65 percent of patients, and nonconvulsive status epilepticus has been reported. Although death or permanent disability can occur, the encephalopathy is usually reversible and can be treated with methylene blue.[2]

Temozolomide

Temozolomide is standard chemotherapy for high-grade gliomas, and common side effects include nausea, fatigue, myelosuppression, and constipation. It rarely produces significant neurologic toxicity, though headaches may occur in up to 40 percent of patients.[3]

TABLE 28-4 ■ Neurotoxicity of Cisplatin

Common	
	Peripheral neuropathy (large fiber, sensory)
	Lhermitte sign
	Hearing loss (high frequency)
	Tinnitus
Uncommon	
	Encephalopathy
	Visual loss (retinal, optic nerve, cortical)
	Seizures
	Herniation (hydration-related)
	Electrolyte imbalance (Ca^{2+}, Mg^{2+}, Na^{+}, SIADH)
	Vestibular toxicity
	Autonomic neuropathy

SIADH, syndrome of inappropriate antidiuretic hormone secretion.

PLATINUMS

The platinums (cisplatin, oxaliplatin, carboplatin) contain a heavy-metal moiety, and they therefore cause a peripheral neuropathy (Table 28-4).

Cisplatin

The peripheral neuropathy associated with cisplatin is dose dependent and usually follows cumulative doses exceeding 400 mg/m^2. It is characterized by numbness and tingling in the extremities, occasionally painful. The first symptoms usually appear during treatment, but typically they progress for several months after therapy is completed. The disorder affects predominantly the large sensory fibers; the deep tendon reflexes disappear and proprioception is lost, often resulting in ataxia. Pain and temperature sensation are spared, and power may be normal. The disorder may be confused with paraneoplastic sensory neuronopathy, which usually affects all sensory modalities equally. Nerve conduction studies reveal a sensory axonopathy. With discontinuation of the drug, the neuropathy may improve and the patient's condition may even return to normal after many months; however, many are left with permanent disability. Because maximal injury is not observed until months after discontinuation of the drug, dose adjustment is not possible to accommodate ongoing neural damage. There is no known treatment and there are insufficient data to support preventative pretreatment with acetylcysteine, acetyl-L-carnitine, amifostine, calcium and magnesium, growth factors, glutathione, Org 2766, oxcarbazepine, or vitamin E.[4]

Lhermitte sign appearing during or shortly after treatment with cisplatin suggests a transient demyelinating lesion in the posterior columns of the spinal cord. In some instances, patients may experience paresthesias down the arms when the upper limbs are abducted, suggesting that the brachial plexus may be demyelinated as well. Lhermitte sign resolves completely and is not associated with any permanent damage.

Muscle cramps not related to electrolyte imbalance (see later) are also common but, like Lhermitte sign, they usually resolve spontaneously.

Ototoxicity is caused by cisplatin. Hearing loss results from hair cell damage. The hearing loss is often subclinical and affects primarily the high-frequency range ($>$4,000 Hz). Tinnitus may precede hearing loss; rarely, high-dose cisplatin causes acute deafness. Animal studies suggest that prophylactic vitamin E or sodium thiosulfate may reduce this toxicity. Human data on amifostine are insufficient to support its use as an otoprotective agent.[4] Radiotherapy that encompasses the VIII nerve complex and hearing apparatus can enhance the ototoxicity of cisplatin regardless of the sequence of the two modalities. Vestibular toxicity is much less common than hearing loss.

Encephalopathy is rare following intravenous infusion, and is characterized by seizures and focal brain dysfunction, particularly cortical blindness, but the symptoms are usually reversible. Encephalopathy due to the drug must be differentiated from the electrolyte disorders that result from its administration. Vigorous hydration precedes cisplatin use and can lead to water intoxication and cerebral herniation. SIADH with hyponatremia and seizures may also occur.

Cisplatin has been implicated in late vascular toxicity, such as Raynaud phenomenon and the cardiac and cerebral infarction that sometimes follows multiagent chemotherapy. Vascular toxicity can also be subacute and occur within days to weeks of cisplatin administration. Other rare complications of cisplatin include irreversible myelopathy, taste disturbances, and a myasthenic syndrome.

Oxaliplatin

Oxaliplatin produces two types of peripheral neuropathy. The first occurs during or shortly after infusion and consists of paresthesias and dysesthesias of the hands, feet, and perioral region with jaw tightness. These symptoms are usually transient, may be triggered by cold, and may increase in both duration and severity with repeated drug administration. A pharyngolaryngeal dysesthesia syndrome accompanied by a sensation of shortness of breath without any objective evidence of respiratory distress has been described. Second, oxaliplatin can induce a peripheral sensory neuropathy similar to that seen with cisplatin. This neurotoxicity generally follows a cumulative dose greater than 540 mg/m^2 and is characterized by sensory ataxia, jaw pain, eye pain, ptosis, leg cramps, visual changes, and voice changes. Although reversible, these clinical findings may persist for months and require discontinuation of treatment. Less common neurologic complications include Lhermitte phenomenon and urinary retention; ototoxicity is rare.

Carboplatin

Carboplatin is less neurotoxic than cisplatin or oxaliplatin. Rare cases of peripheral neuropathy can occur but usually after high doses of carboplatin in patients treated with combinations of other cytotoxic agents.

Monoclonal Antibodies

BEVACIZUMAB

Bevacizumab is a monoclonal antibody that binds to and inhibits soluble vascular endothelial growth factor (VEGF), a mediator of tumor angiogenesis.[5] Patients treated with bevacizumab have an increased incidence of systemic hemorrhages as well as venous thromboembolism. Arterial thromboembolism is also seen, albeit uncommonly, including stroke and transient ischemic attacks (TIAs). The risk of CNS hemorrhage in patients with glioblastoma is under 4 percent, and comparable to the risk associated with the disease itself. Bevacizumab's most common side effect is hypertension, which rarely may lead to posterior reversible encephalopathy syndrome (PRES) in some patients. Symptoms include headache, lethargy, visual disturbances including blindness, and seizures. Symptoms usually resolve with discontinuation of the drug and with blood pressure control, though permanent deficits can occur. Rarely, bevacizumab may cause visual loss due to optic neuropathy.

RITUXIMAB

Rituximab is a monoclonal antibody directed against the CD20 antigen found on the surface of malignant and normal B lymphocytes. It is used to treat non-Hodgkin lymphoma as well as other disorders in which B lymphocytes are implicated in disease pathogenesis. Neurologic side effects are uncommon but can include myalgias, dizziness, and headache. Rituximab has also rarely been associated with PML.

Small-Molecule Inhibitors

BORTEZOMIB AND CARFILZOMIB

Bortezomib is a proteosome inhibitor that is primarily effective against multiple myeloma. It causes a cumulative dose-dependent painful peripheral neuropathy that is predominantly sensory, but is also associated with enhanced vulnerability to pressure-point neuropathies, such as peroneal nerve compression.[4] Symptoms usually improve, even without stopping treatment, but some patients are left with fixed deficits. Carfilzomib is a second-generation proteasome inhibitor; it causes a peripheral neuropathy that tends to be less severe than bortezomib.

SELUMETINIB

Selumetinib is a small-molecule inhibitor of MEK, a mitogen-activated protein kinase, used in clinical trials against solid tumors and melanoma. It can cause dropped head syndrome, a focal noninflammatory myopathy characterized by neck pain, neck extensor weakness, and elevated serum creatine kinase levels. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan may show abnormal uptake in the affected muscles. Corticosteroids do not improve the condition, but discontinuation of the drug leads to recovery.

Retinoids

The retinoids are a group of compounds consisting of vitamin A and related derivatives. They are used to treat acute promyelocytic leukemia (APL) as well as other malignancies. Headaches may occur, sometimes in association with intracranial hypertension, but headaches may occur independently as well. There may be an increased risk of suicide and depression in patients treated with retinoids, although this is currently unclear.

Immunotherapy

The term *cancer immunotherapy* encompasses a variety of different treatment strategies designed to harness the power of the body's own immune system and alter it to target cancer cells more effectively for therapeutic purposes. While immunotherapy has revolutionized cancer care for many patients, these therapies have been associated with several different and novel neurotoxicities. As the number of available agents grows and the number of approved indications grows as well, vigilance is necessary for the detection of neurotoxicity, as early detection and management often mitigate toxicity severity and duration. Although different immunotherapy strategies exist, the two main treatments discussed here are with the checkpoint inhibitors (CPIs) and chimeric antigen receptor (CAR) T cells.

CHECKPOINT INHIBITORS

Treatment with CPIs has improved the outcome of patients with a variety of cancers. They work by targeting normal checkpoints in the immune system that would typically suppress an immune response. Cancers often find ways to exploit these immunosuppressive mechanisms, and CPIs aim to block these inhibitory pathways, thereby "unleashing" the immune system to attack the cancer. Approved therapies include those that target the checkpoints cytotoxic T-lymphocyte-associated-4 (CTLA-4; ipilimumab and atezolizumab), programmed cell death protein 1 (PD-1; nivolumab and pembrolizumab), and its ligand on cancer cells (PD-L1; durvalumab, avelumab, and cemiplimab).

Neurologic toxicities with these drugs are similar across the entire class and are discussed in aggregate. Neurologic toxicities are uncommon, occurring in 1 to 5 percent of patients treated with CPIs, but may be severe. Because of the mechanism of action of these drugs, their side effects are unlike those seen with other chemotherapies. Toxicities result from activation of the immune system having a secondary effect on the nervous system, and can include myasthenia gravis, Guillain–Barré syndrome, peripheral neuropathy, autonomic neuropathy, aseptic meningitis, encephalitis, transverse myelitis, vasculitis, myositis, and PRES.[6,7] Vigilance, early detection, and intervention with corticosteroids are key to treatment and possible reversibility of toxicity. It is often necessary to discontinue CPI treatment.

CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPIES

CAR T-cell therapy has similarly transformed the care of many patients with hematologic malignancies and is under development for the treatment of solid tumors as well. CAR T cells utilize a technology whereby a patient's own T cells are removed, modified to recognize a specific cancer cell target, expanded, and then infused back into the patient. CAR T cells offer a unique therapeutic approach for patients, but also may cause unique toxicities, including the cytokine release syndrome (CRS) and a specific form of neurologic toxicity, described here.

CRS is the result of an overly robust immune activation due to supraphysiologic elevation of cytokines.[8] Encephalopathy may accompany the systemic manifestations of CRS, such as fever, hypotension, nausea, and chills, which typically occur a few hours to a week after CAR infusion. Separately from CRS, patients may develop a specific CAR T-cell–related neurotoxicity which may be severe, occurs either during or after CRS, and is the second major adverse event seen with CAR T-cell therapy. Although much of the toxicity is self-limited and reversible, it can be severe and, rarely, fatal. As the number of cellular therapeutic products has increased (e.g., bispecific antibodies), the neurotoxicity associated with these immune modulators is now referred to as immune effector cell-associated neurologic syndrome (ICANS).

The most common neurologic symptoms include encephalopathy, aphasia, delirium, tremor, seizures, and, in rare cases, a potentially fatal, rapidly progressive cerebral edema.[9] The syndrome may also include headache, lethargy, difficulty concentrating, anxiety, sleep disorder, dizziness, ataxia, and motor dysfunction. As with CPI neurotoxicity, vigilance and early detection are key to successful treatment. Certified CAR T-cell centers have a clear algorithm to manage such toxicity including with corticosteroids, reversing agents, and "suicide switch" activating compounds.

Intrathecal Chemotherapy

Chemotherapy is sometimes given directly into the subarachnoid space as part of treatment for or prophylaxis against leptomeningeal metastases. It can either be injected into the lumbar thecal sac via lumbar puncture or into the lateral ventricle through an Ommaya reservoir. Intrathecal chemotherapy is contraindicated in patients who have elevated intracranial pressure (ICP). Increased ICP may cause plateau waves, which consist of waves of elevated ICP associated with transient neurologic symptoms such as visual changes, leg buckling, vertigo, or loss of consciousness in the setting of positional change or Valsalva maneuver. In patients with elevated ICP, intrathecally administered chemotherapy will not circulate properly through the CSF and may accumulate in the ventricle, causing toxicity when administered through an Ommaya reservoir.

Intrathecal methotrexate causes an aseptic meningitis in 10 to 50 percent of patients, primarily after administration by lumbar puncture rather than via ventricular cannula.[10] Patients complain of headache, nausea, vomiting, and neck stiffness, and can become febrile and lethargic. Symptoms usually begin 2 to 4 hours after drug administration and can last up to a few days (Table 28-5). A CSF pleocytosis is often present and can mimic acute bacterial meningitis, except that it occurs too soon after injection to be caused by bacterial growth. The symptoms are self-limited, and there is no specific treatment, though corticosteroids can reduce the inflammation and have been used as therapy. The drug may be readministered without recurrent aseptic meningitis, and prophylactic oral corticosteroids may help. Transverse myelopathy is a less common complication of intrathecal methotrexate. The symptoms include back pain followed by weakness, sensory changes, and sphincter dysfunction; they usually start between 30 minutes and 2 days after drug administration, but can be delayed by up to 2 weeks.[1] Concurrent radiotherapy may be a risk factor. Recovery may be incomplete and further intrathecal chemotherapy is contraindicated.[10] Acute encephalopathy is rare, but can occur if the intraventricular catheter is misplaced into the brain parenchyma rather than in the ventricle. Other complications include seizures, cranial neuropathies, PRES, lumbosacral polyradiculopathy, and sudden death.

TABLE 28-5 ■ Methotrexate Toxicity*

Route of Administration	Dose	Toxic Effect
Oral or intravenous	Standard	Leukoencephalopathy
Intravenous	High	Acute transient encephalopathy Chronic leukoencephalopathy
Intra-arterial	Standard	Hemorrhagic cerebral infarction
Intrathecal	Standard	Acute aseptic meningitis, paraplegia, seizures Chronic leukoencephalopathy, cerebral atrophy, and calcification

*Toxicity may be enhanced by cranial irradiation and/or other systemic chemotherapeutic agents.

Cytarabine intrathecally can also cause aseptic meningitis in approximately 10 percent of patients. Aseptic meningitis occurred in more patients (40%) when the cytarabine was given as the liposomal preparation, DepoCyt, but this is no longer available. Dexamethasone should be taken prophylactically at a dose of 4 mg twice daily for 5 days, starting the day prior to administration, to decrease the risk of aseptic meningitis and arachnoiditis. Transverse myelopathy can develop a few days to months following treatment. Other complications include seizures, headaches, and encephalopathy.

Intrathecal thiotepa can cause aseptic meningitis and rarely a myelopathy. Topotecan intrathecally can cause aseptic meningitis and, less commonly, seizures as well as leukoencephalopathy.

Rituximab is given intrathecally to treat leptomeningeal lymphoma. Headache, cramps, and reversible back pain associated with paraparesis can occur, as well as neuropathic pain, leukoencephalopathy, transient diplopia, nausea and vomiting, and paresthesias. Intrathecal traztuzumab has been used for leptomeningeal metastases from HER2-positive breast cancer. Aseptic meningitis has not been reported with intrathecal rituximab or traztuzumab, but use of those drugs via the intrathecal route is relatively recent.

RADIATION THERAPY

Therapeutic ionizing irradiation may damage neural structures when they are included in the radiation portal, whether the cancer undergoing RT is within or outside the nervous system. Nervous

TABLE 28-6 ■ Radiation-Induced Injury: Direct Damage to the Central Nervous System

Time After Radiation	Clinical Findings	Possible Mechanisms
Brain		
Acute (minutes to days)	Increased intracranial pressure	Acute vasogenic edema
Early delayed (weeks)	Pseudoprogression Brainstem encephalopathy Somnolence syndrome	Demyelination
Delayed (months to years)		
Necrosis	Diffuse: dementia (rare) Focal: simulates recurrent tumor	Glial and vascular destruction
Leukoencephalopathy	Asymptomatic or dementia	Unknown Atrophy Spongiosis of white matter Normal-pressure hydrocephalus
Spinal Cord		
Early delayed (weeks)	Lhermitte sign	Demyelination
Delayed (months to years)		
Spinal cord necrosis	Transverse myelopathy	Glial and vascular destruction
Motor neuron disease	Flaccid paraparesis, amyotrophy	Unknown
Arachnoiditis	Often asymptomatic	Radiation-induced damage to the leptomeninges
Hemorrhage	Acute myelopathy	Vascular lesions

system injury can also occur secondarily when irradiation damages blood vessels supplying the brain or the endocrine organs necessary for normal nervous system function, or when the irradiation causes tumors that compress or destroy nervous system structures. Nervous system dysfunction caused by RT can occur acutely or may be delayed by weeks, months, or even years following the successful completion of treatment. The likelihood that RT will damage the nervous system depends on the total dose delivered to the nervous system, the dose per fraction, the total volume of nervous system irradiated, the time after completion of RT, the presence of other systemic diseases that enhance the side effects of irradiation (e.g., diabetes, hypertension), and other unidentifiable host factors. Detailed reviews of RT-induced neurotoxicity can be found elsewhere.[1,11]

Primary Neurologic Damage

BRAIN

Encephalopathy caused by RT occurs in three forms: acute, early delayed (weeks to months), and late delayed (months to years), as summarized in Table 28-6.

Acute Encephalopathy

Acute encephalopathy usually follows large RT fractions given to patients with increased ICP from primary or metastatic brain tumor, particularly in the absence of corticosteroid coverage.[1] Immediately following treatment, susceptible patients develop headache, nausea, vomiting, somnolence, fever, and worsening of neurologic symptoms, rarely severe enough to culminate in cerebral herniation and death. Acute encephalopathy usually follows the first radiation fraction and becomes progressively less severe with each ensuing fraction. Usually, the disorder is mild, with the patient developing headache and nausea in the evening following irradiation.

The pathogenesis of the disorder is uncertain. There are variable data to suggest it is secondary to a rise in ICP, with cerebral edema following breakdown of the blood–brain barrier by ionizing irradiation, particularly with fractions of 300 cGy or more. Therefore, patients harboring large brain tumors, particularly with signs of increased ICP, should be treated with doses of 200 cGy or less per fraction. All patients undergoing brain irradiation should be protected with corticosteroids (8 to 16 mg of dexamethasone daily) preferably for at least 24 hours before the start of RT. Both clinical and experimental evidence indicate that corticosteroids ameliorate the acute complications of irradiation.

Early Delayed Encephalopathy

Early delayed encephalopathy, which is thought to be due to demyelination, usually begins in the second or third month after irradiation but can begin anywhere from 2 weeks to 4 months after treatment. If the patient has a glioblastoma, the symptoms of early delayed encephalopathy often simulate tumor progression ("pseudoprogression"). The risk of pseudoprogression is increased in those patients whose tumor contains a methylated promoter of the O^6-methylguanine-DNA methyltransferase (*MGMT*) gene, a DNA repair enzyme. For example, the patient may develop recurrence of headache, lethargy, and worsening of lateralizing signs. Changes on neuroimaging may include an increase in size of the lesion and sometimes the new appearance of contrast enhancement. These changes resolve spontaneously if the disorder is due to radiation encephalopathy rather than tumor recurrence, and the resolution can be hastened by corticosteroids. The patient and the scan remain improved after corticosteroids are discontinued, indicating that the disorder was not tumor recurrence.

A rare and serious early delayed neurologic syndrome is brainstem encephalopathy following irradiation of posterior fossa tumors or when the brainstem has been included in the irradiated field for head and neck cancer. The most frequent symptoms are ataxia, diplopia, dysarthria, and nystagmus. Most patients recover spontaneously within 6 to 8 weeks. Rarely, the symptoms progress to stupor, coma, and death.

Late Delayed Radiation Injury

Radiation Necrosis

Late delayed radiation necrosis usually begins 1 to 2 years after the completion of RT. In patients who are treated for primary or metastatic brain tumors, symptoms generally recapitulate those of the brain tumor, leading the physician to suspect tumor recurrence. A second clinical picture occurs when the patient's brain was included in the radiation portal, but there was no underlying brain tumor. Examples include irradiation of head and neck tumors, including pituitary tumors, and prophylactic cranial irradiation.[1] Because only a portion of the brain has usually been irradiated and there was no previous brain damage, new focal neurologic signs are the rule. For example, bilateral medial temporal destruction sometimes follows irradiation for nasopharyngeal or pituitary tumors, and frontal or temporal lobe destruction follows treatment for ocular or maxillary sinus tumors. The clinical features are similar to those of a brain tumor, with focal signs, depending on the site of brain damage, and increased ICP if the lesion is sufficiently large. The MRI usually reveals a mass, often with contrast enhancement (Fig. 28-2). FDG-PET, MR spectroscopy, and advanced MRI sequences may help differentiate between necrosis and tumor. Elevated cerebral blood volume on MR perfusion sequences, restricted diffusion with hypointensity on ADC images of MRI, and hypermetabolism on FDG-PET all favor recurrent tumor rather than radiation necrosis, but a definitive diagnosis can be made only pathologically.

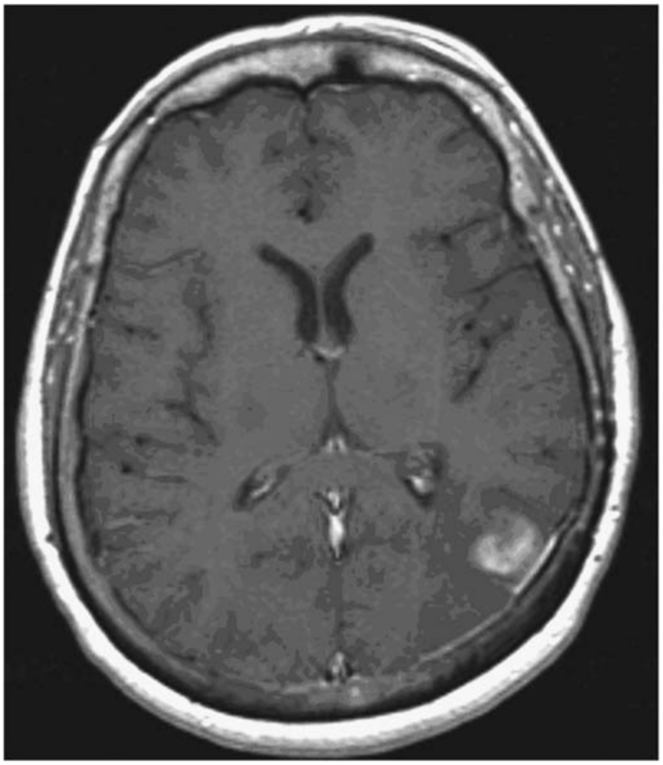

FIGURE 28-2 ■ Radiation necrosis. T1-weighted, postcontrast MRI 9 months after stereotactic radiosurgery for a left parietal, dural-based metastasis. The lesion was hypointense on precontrast T1-weighted sequences.

Radiation necrosis is often treated initially with corticosteroids; however, patients may respond only transiently. Bevacizumab has also shown clinical and radiographic benefit in the treatment of radiation necrosis and can allow steroid dosage to be decreased. When patients are symptomatic despite medical therapy or they develop morbidity from treatment, radiation necrosis may be treated by surgical resection. Other suggested treatments, such as vitamin E, pentoxifylline, hyperbaric oxygen, antiplatelet agents, and anticoagulation, are based on the rationale that the disorder is characterized by fibrinoid necrosis of vessels, but they have not proved useful in most patients.

SMART Syndrome

Stroke-like migraine attacks after RT, or SMART syndrome, are a rare complication of cranial irradiation that may occur 1 to 10 years after treatment. The syndrome is characterized by migraine-like headaches associated with transient neurologic signs, which may be accompanied by seizures. MRI may show focal contrast enhancement that resolves over time without intervention.[12] The mechanism is thought to be due to neuronal dysfunction, and not cerebral vascular activity.

Cerebral Atrophy

Cerebral atrophy often follows whole-brain irradiation, and it may be accompanied by periventricular leukoencephalopathy. The atrophy may occur in patients irradiated prophylactically or in those with a brain tumor that was eradicated by radiotherapy. It usually begins 6 to 12 months after RT. The patient may be asymptomatic or suffer memory loss, which may be severe. Some patients have gait abnormalities and urgency incontinence, suggesting normal-pressure hydrocephalus, and they may respond to ventriculoperitoneal shunt. Symptomatic patients generally have greater degrees of atrophy and ventricular dilatation than asymptomatic patients. Cerebral atrophy occurs in children receiving prophylactic brain irradiation for acute leukemia, and it is associated with learning disabilities.

SPINAL CORD

There are no acute effects of radiation on the spinal cord.

Early Delayed Radiation Myelopathy

Early delayed radiation myelopathy is common after irradiation of the neck (Table 28-6). Several weeks after irradiation, the patient develops Lhermitte sign that persists for weeks or months and then disappears spontaneously. This may be associated with delayed somatosensory evoked potentials. Symptoms are thought due to demyelination of the posterior columns of the spinal cord, but they do not predict the development of late delayed radiation spinal cord injury.

Late Delayed Radiation Myelopathy

Late delayed radiation myelopathy appears in two forms. The first and most common is characterized by progressive myelopathy, often beginning as a Brown-Séquard syndrome and progressing over weeks or months to cause paraparesis or quadriparesis. Usually the symptoms progress subacutely, but in some instances they progress over several years and, at times, may stabilize, leaving the patient with only mild or moderate paraparesis. MRI is usually nonspecific but helps to exclude metastatic spinal cord compression or intramedullary metastasis. Hyperintense changes of the irradiated vertebral bodies due to fat replacement of bone marrow may outline the radiation field even if the details of the RT port are unknown. In the acute stages the spinal cord is swollen and the damaged area may enhance with contrast material; spinal cord atrophy develops later. There is no good treatment, although corticosteroids sometimes delay progression of the lesion. Other potential therapies include hyperbaric oxygen and anticoagulation but they do not give benefit reliably.

A second form of late delayed radiation myelopathy is a rare motor neuron syndrome that characteristically follows pelvic irradiation or after craniospinal irradiation for medulloblastoma.[13] This disorder occurs 3 months to 23 years following irradiation and is characterized by the subacute onset of flaccid leg weakness affecting both distal and proximal muscles accompanied by atrophy, fasciculations, and areflexia. It is usually bilateral and symmetric but may be asymmetric or restricted to one leg. Sensory, sphincter, and sexual functions are normal. The CSF may contain an increased protein concentration. Imaging is typically normal. Although electromyography reveals varying degrees of denervation, sensory and motor nerve conduction velocities are normal. It is difficult to differentiate the disorder from a pure motor polyneuropathy, isolated motor neuron loss, or the paraneoplastic syndrome of subacute motor neuronopathy. The deficit usually stabilizes after several months to a few years; often patients are still able to walk, but some may become paraplegic.

Another lower motor neuron syndrome caused by irradiation is dropped head syndrome, which can occur after mantle radiation in the treatment of Hodgkin lymphoma. Amyotrophy of the neck and shoulder muscles is associated with reduced cervical range of motion, weakness in the neck flexors and extensors, neck pain, and a posture in which the head is dropped forward and resting on the chest.

CRANIAL NERVES

The clinical features of radiation injury to the cranial and peripheral nerves and the special senses are shown in Table 28-7. Anosmia may follow irradiation. Taste is affected in almost every patient who undergoes cranial radiotherapy. Visual loss may follow irradiation of the eye or brain. It may be caused by radiation-induced "dry eye syndrome," glaucoma, or cataract; more commonly, it result from retinopathy or optic neuropathy. The optic neuropathy following irradiation begins 7 to 26 months after RT and is characterized by painless monocular or bilateral blindness. Papilledema and retinal hemorrhages may be present. Hearing loss may also follow RT to the brain or ear. Radiation-induced otitis media appears during or shortly following cranial RT and causes a conductive hearing loss that may require myringotomy for relief. It is different from the sensorineural hearing loss that is a late delayed RT effect and that has been attributed to an endarteritis producing vascular damage of the cochlear or acoustic nerve.[1] The lower cranial nerves, particularly the hypoglossal nerves, are often involved as a late delayed effect of RT delivered to the neck. Lower cranial neuropathy can be delayed for over 10 years. Electrophysiologic studies commonly show myokymia and myokymic discharges. Recurrent laryngeal, vagal, and sympathetic fibers (Horner syndrome) may be involved as well.

TABLE 28-7 ■ Radiation-Induced Injury: Damage to the Cranial and Peripheral Nerves and Organs of Special Sense

Cranial Nerves

- Visual system
  - Retinopathy
  - Optic neuropathy
  - Central retinal artery occlusion
- Taste and smell
  - Acute, transient loss of taste and smell during radiation therapy
  - Chronic loss of smell (rare)
- Involvement of the lower cranial nerves
  - Twelfth nerve most frequently affected

Brachial Plexus Neuropathies

- Acute?
- Early delayed (rare)
- Delayed brachial plexopathy

Delayed Lumbosacral Plexopathy

PERIPHERAL NERVES

There are no acute changes in peripheral nerve function following RT. Early delayed brachial plexus dysfunction is characterized by paresthesias in the hand and forearm, sometimes associated with pain and accompanied by weakness and atrophy in a C6 to T1 distribution.[1] Nerve conduction studies reveal segmental slowing, and the course is characterized by recovery over a few weeks or months. This disorder is particularly common in patients with breast cancer because the brachial plexus is frequently included in the radiotherapy port of the primary cancer.

Late delayed radiation plexopathy has been reported after irradiation of either the brachial[1] or lumbosacral plexus, although the former is more common. The disorder usually occurs a year or more after RT doses of or exceeding 5,000 cGy. Brachial plexopathy is characterized by paresthesias and weakness of the hand or arm. Sensory loss, particularly in the fingers and hand, is seen early but the numbness and weakness often progress to a complete plexopathy, rendering the entire arm useless. This disorder is frequently accompanied by lymphedema and palpable induration in the supraclavicular fossa. Radiation-induced plexopathy is usually painless, which distinguishes it from tumor plexopathy, which is typically painful. Myokymia on electrodiagnostic testing in the territory of affected nerves is characteristic of radiation damage as opposed to tumor infiltration of the plexus. CT scan or MRI usually reveals a diffuse loss of tissue planes without a mass. Occasionally, radiation damage can produce a marked fibrotic reaction causing a mass of fibrosis that cannot be distinguished from tumor, but FDG-PET discriminates tumor from fibrosis. There is no treatment for radiation plexopathy, although painful paresthesias may be relieved by amitriptyline or gabapentin (or other treatments for neuropathic pain).

Lumbosacral plexopathy causes painless weakness of one or both legs. The disorder often affects the foot, and sensory impairment as well as weakness is present in most cases. Electromyography frequently reveals myokymic discharges, which differentiate the process from tumor recurrence. Radiation-induced lumbosacral plexopathy is often slowly progressive over many years. The pathogenesis of RT plexopathy is thought to be related to fibrosis causing damage to Schwann cells, rather than stemming from direct damage to the nerves themselves.

Secondary Neurologic Involvement

Radiogenic Tumors

The manner in which the nervous system may be affected secondarily after RT is summarized in Table 28-8.

TABLE 28-8 ■ Secondary Involvement of the Nervous System Following Radiation Therapy

Radiation-Induced Tumors
Meningiomas–atypical, malignant
Sarcomas–malignant
Gliomas–malignant
Schwannomas–malignant
Vascular Lesions
Stenosis/occlusion of the supraclinoid internal carotid
Moyamoya syndrome
Extracranial stenosis/occlusion
Carotid rupture (rare)
Endocrinopathy
Primary hypothyroidism
Hyperparathyroidism
Hypothalamic pituitary dysfunction
Growth hormone deficiency (most frequent)
Hyperprolactinemia
Cortisol deficiency (rare)
Gonadotropin deficiency (rare)

Radiation-induced tumors, including meningiomas, sarcomas, and, less frequently, gliomas and malignant schwannomas, may appear years to decades after irradiation of nervous system tissue; secondary tumors may develop even after low doses of RT. Children who received low-dose scalp RT for tinea capitis had an increase in the incidence of meningiomas and higher rates of multiple meningiomas and recurrence compared to nonirradiated control patients. Malignant or atypical nerve sheath tumors may follow irradiation of the brachial, cervical, or lumbar plexuses. Signs and symptoms of radiogenic tumors are no different from tumors that arise without prior RT, and their surgical treatment is similar. Some patients may be able to tolerate additional RT or chemotherapy if the tumor is malignant and cannot be excised totally.

Vascular Abnormalities

Atherosclerosis of large intracranial or extracranial blood vessels may follow RT by months to years. Patients may develop TIA or cerebral infarcts. Arteriography reveals stenosis or occlusion of the artery within the radiation portal. A particularly vulnerable area is the supraclinoid portion of the internal carotid artery in children who received brain irradiation; this occlusion is sometimes associated with moyamoya syndrome. The pathology of radiation-induced vascular occlusion is similar to severe atherosclerosis, although there may be marked periarterial fibrosis as well. This condition is characterized by atherosclerosis restricted to the vessel segment within the RT field without evidence of widespread involvement elsewhere, by the younger age of the affected patients, and by the atypical location of the stenotic carotid segments. If appropriate, endarterectomy or carotid stenting can be performed successfully on patients with extracranial vascular disease.

Cavernomas may also develop as a complication of cranial or spinal RT, occurring as early as 1 year after treatment but typically many years later. They may be at higher risk of bleeding compared to cavernomas unassociated with prior RT (Fig. 28-3).

A few patients have been described with hemorrhage in the spinal cord developing many years after

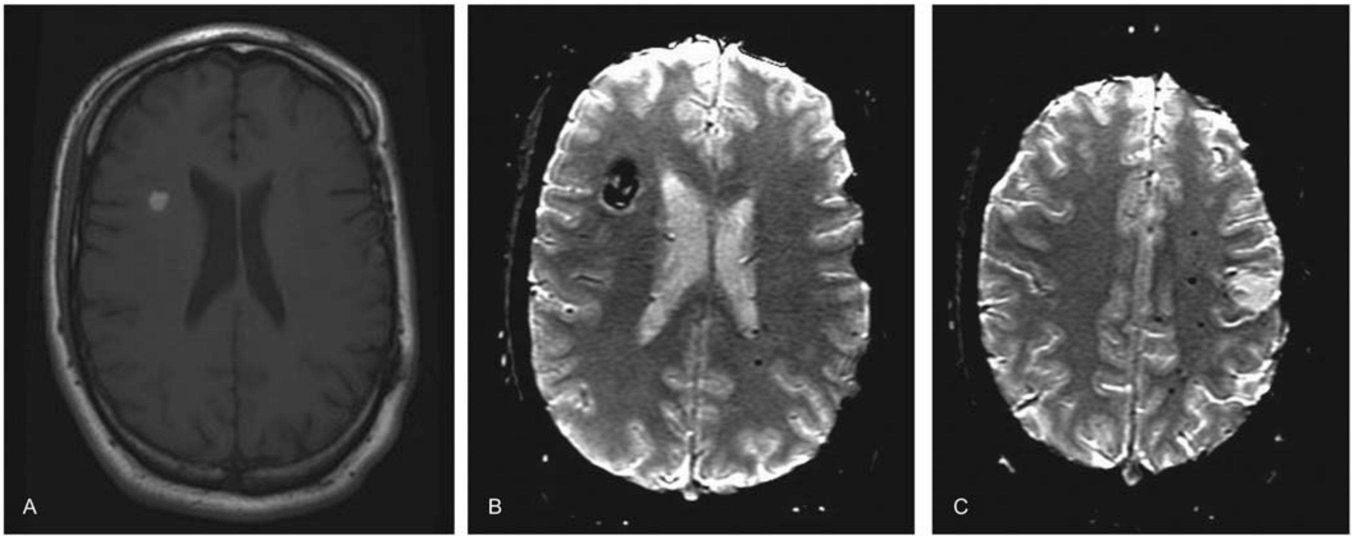

FIGURE 28-3 ■ Radiation-induced cavernomas (images *A*–*C* are different sequences from the same MRI). *A*, T1-weighted, precontrast MRI 6 years after focal radiation for a left frontal grade 2 astrocytoma, showing hemorrhage. *B*, Susceptibility-weighted imaging (SWI) demonstrating a hemorrhagic cavernoma in the right frontal lobe. *C*, SWI demonstrating multiple microbleeds in the left hemisphere.

irradiation. Characteristically, 8 to 30 years after RT to the spine, a patient without prior neurologic symptoms suddenly develops back pain and leg weakness. MRI suggests acute or subacute hemorrhage, but no other lesions are found. The patient typically improves, and the symptoms may resolve entirely. A few patients have had recurrent episodes of spinal cord hemorrhage. The pathogenesis is probably related to telangiectatic vascular changes caused by the RT, but anecdotally we have noticed that hemorrhage is often preceded by heavy use of nonsteroidal anti-inflammatory drugs.

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SECTION

9

Genitourinary System and Pregnancy

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CHAPTER

29

Lower Urinary Tract Dysfunction and the Nervous System

AMIT BATLA ■ JALESH N. PANICKER

NEUROLOGIC CONTROL OF THE BLADDER
- Brain Centers
- Innervation of the Lower Urinary Tract
- Storage Phase
- Voiding Phase
- Central Mediation of Voiding
- Neurochemistry of the Urothelium and Bladder Pharmacology

NEUROGENIC BLADDER DYSFUNCTION
- Cerebral Lesions
- Basal Ganglia Lesions
  - *Parkinson Disease*
  - *Multiple System Atrophy*
- Brainstem Lesions
- Spinal Cord Lesions
- Bladder Dysfunction in Multiple Sclerosis
- Disturbances of Peripheral Innervation
  - *Diabetic Neuropathy*
  - *Amyloid Neuropathy*
  - *Immune-Mediated Neuropathies*
  - *Autoimmune Autonomic Ganglionopathy*
  - *Pure Autonomic Failure*
- Myotonic Dystrophy
- Urinary Retention
  - *Fowler Syndrome*

DIAGNOSTIC EVALUATION
- History
- Bladder Diary
- Physical Examination

INVESTIGATIONS
- Bladder Scan
- Screening for Urinary Tract Infections
- Ultrasound Scan
- Urodynamic Studies
  - *Noninvasive Bladder Investigations*
  - *Investigations Requiring Catheterization*
- Pelvic Neurophysiology
  - *Electromyography*
  - *Pudendal Somatosensory Evoked Potentials*

COMPLICATIONS OF NEUROGENIC BLADDER DYSFUNCTION

MANAGEMENT OF NEUROGENIC BLADDER DYSFUNCTION
- Management of Voiding Dysfunction
- Management of Storage Dysfunction
  - *General Measures*
  - *Antimuscarinic Medications*
  - *Beta-3 Receptor Agonists*
  - *Desmopressin*
  - *Cannabinoids*
  - *Botulinum Toxin*
  - *Vanilloids*
  - *Nerve Stimulation*
  - *Surgery*
  - *Permanent Indwelling Catheters*
- Stepwise Approach to Neurogenic Bladder Dysfunction

Lower urinary tract dysfunction is common in patients with neurologic disease. The neurogenic bladder can result from lesions affecting any part of the nervous system. Symptoms are often bothersome and may have a significant impact on quality of life. Some patients may also be at risk of developing changes in the upper urinary tract and even renal impairment.

NEUROLOGIC CONTROL OF THE BLADDER

The essential function of the lower urinary tract (bladder and urethra) is storage of urine and its elimination at appropriate times. This function ultimately depends on a local spinal reflex arc which is regulated by supraspinal input to preserve continence until appropriate.

Neurologic control of the key bladder functions of storage and voiding is accomplished by a neural network involving regions of the cortex, brainstem, and spinal cord. The peripheral innervation of the detrusor and sphincter is vital in the execution of this central control. Understanding of the neurologic control of the bladder was derived initially from animal studies, and then refined using functional imaging studies.[1] Experiments on decerebrate cats in the

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1920s led to the understanding that the mid-pons played an integral role in micturition. This same region was later stimulated electrically in cats to produce detrusor contractions. Subsequent work demonstrated that stimulation of the medial region of the dorsomedial pontine tegmentum led to relaxation of urethral pressure, silence of the pelvic floor electromyogram, and an increase of detrusor pressures; as a result, this area became known as the pontine micturition center. Later studies established functional continuity of the intermediolateral cell column in the sacral spinal cord to this region.

Brain Centers

The development of functional imaging modalities such as positron emission tomography (PET) and functional magnetic resonance imaging (MRI) has allowed further understanding of the central control of micturition.[1,2] Activation occurs in the region of the medioposterior pons during voiding and in the region of the ventrolateral pontine tegmentum in subjects unable to void in the scanner. In the cortex, PET studies have suggested that the right inferior frontal gyrus and the right anterior cingulate gyrus are activated during voiding along with several other regions including the cerebellum, hypothalamus, thalamus, subthalamic nucleus, and the periaqueductal gray.

Innervation of the Lower Urinary Tract

The bladder is one of the few visceral organs with voluntary control; it receives innervation from both the autonomic and somatic systems (Fig. 29-1). Parasympathetic fibers arise from neurons in the S2 to S4 segments, activating muscarinic receptors of the detrusor muscle. Sympathetic fibers from the thoracolumbar segments (T11 to L1) pass through the hypogastric nerve and pelvic plexus and activate the β3 receptors of the detrusor muscle and α-adrenergic receptors of the internal urethral sphincter and bladder neck. Somatic fibers pass through the pudendal nerve and activate nicotinic receptors of the external urethral (and anal) sphincter. Sensations of bladder fullness are conveyed to the spinal cord through all these sets of nerves.

Storage Phase

The bladder is in the storage phase 98 percent of the time. During this phase, passive distension of the bladder results in low-level afferent firing. This firing leads to reflex inhibition of parasympathetic efferents and activation of both the sympathetic outflow innervating the internal urethral sphincter and pudendal outflow innervating the external urethral sphincter; these responses promote continence. Ascending afferent signals relay at the periaqueductal gray before reaching cortical centers. Signals from the pontine micturition center are essentially inhibitory and promote storage.

Voiding Phase

When the bladder is perceived to be full and it is a socially appropriate time and place to void, facilitatory signals from the pontine micturition center result in parasympathetically mediated contractions of the detrusor muscle and inhibition of the sympathetic and pudendal outflow (leading to sphincter relaxation).

Central Mediation of Voiding

The decision to void is based on a combination of factors, including emotional state, an appreciation of the social environment, and sensory signals arising from the bladder. Knowledge of the extent to which one's bladder content is comfortable and "safe" is central in this process. Thus, voluntary control of the bladder and the urethra has two important aspects: registration of bladder filling sensations and manipulation of the firing of the voiding reflex, both of which are dependent on the periaqueductal gray.

Neurochemistry of the Urothelium and Bladder Pharmacology

The urothelium (the bladder epithelium) has specialized sensory and signaling properties that allow the bladder to respond to chemical and mechanical stimuli and to engage in reciprocal chemical communication with nerves in the bladder wall. The urothelium expresses nicotinic, muscarinic, tachykinin, adrenergic, bradykinin, and transient-receptor-potential vanilloid receptors. It has the ability to release chemical mediators such as adenosine triphosphate (ATP), acetylcholine (ACh), and nitric oxide,

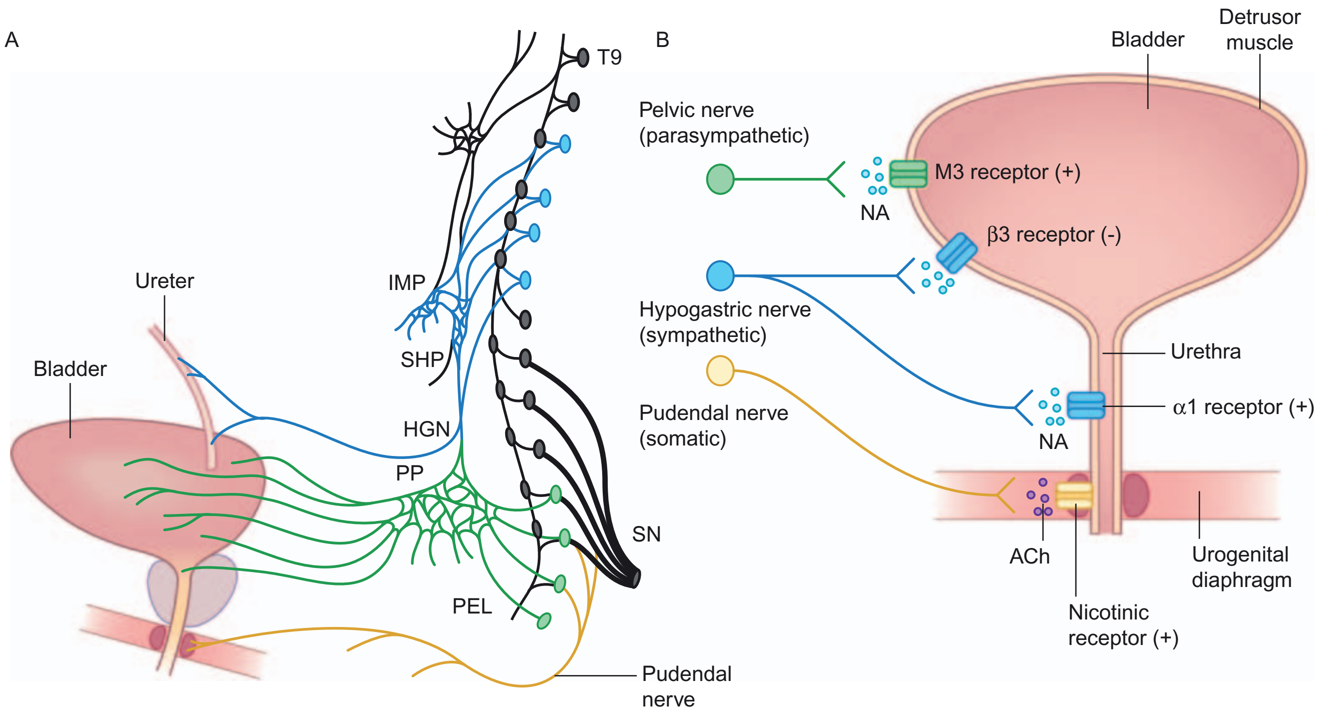


FIGURE 29-1 ■ Innervation of the lower urinary tract. *A*, Sympathetic fibers (shown in blue) originate in the T11–L2 segments in the spinal cord and run through the inferior mesenteric ganglia (inferior mesenteric plexus, IMP) and the hypogastric nerve (HGN) or through the paravertebral chain to enter the pelvic nerves at the base of the bladder and the urethra. Parasympathetic preganglionic fibers (shown in green) arise from the S2 to S4 spinal segments and travel in sacral roots and pelvic nerves (PEL) to ganglia in the pelvic plexus (PP) and in the bladder wall, which then supply parasympathetic innervation to the bladder. Somatic motor nerves (shown in yellow) that supply the striated muscles of the external urethral sphincter arise from S2 to S4 motor neurons and pass through the pudendal nerves. SHP, Superior hypogastric plexus; SN, sciatic nerve; T9, ninth thoracic root. *B*, Efferent pathways and neurotransmitter mechanisms that regulate the lower urinary tract. Parasympathetic postganglionic axons in the pelvic nerve release acetylcholine (ACh), which produces a bladder contraction by stimulating M3 muscarinic receptors in the bladder smooth muscle. Sympathetic postganglionic neurons release norepinephrine (NA), which activates β3 adrenergic receptors to relax bladder smooth muscle and activates β1 adrenergic receptors to contract urethral smooth muscle. Somatic axons in the pudendal nerve also release ACh, which produces a contraction of the external sphincter striated muscle by activating nicotinic cholinergic receptors. (From Fowler CJ, Griffiths D, de Groat WC: The neural control of micturition. Nat Rev Neurosci 9:453, 2008, Part (A) modified from de Groat WC. pp. 28–42. In Raz S (ed): Female Urology. 2nd Ed, Saunders, Philadelphia, 1996.)

which can regulate the activity of adjacent nerves and trigger local vascular changes or reflex bladder contractions.

The presence of muscarinic and nicotinic receptors in the urothelium has focused attention on the role of ACh as a chemical mediator of neural–urothelial interactions. ACh is released from the urothelium in response to chemical or mechanical stimuli. Thus, the clinical effect of antimuscarinic agents in overactive bladder conditions might not only lead to a motor response, but also influence the afferent pathway.[3]

Various neurotransmitters have been implicated in the central control of the lower urinary tract. Putative excitatory transmitters include glutamate, tachykinins, pituitary-adenylate-cyclase-activating polypeptide, nitric oxide, and ATP. Glutamate seems to be the essential transmitter in spinal and supraspinal reflex pathways that control the bladder and the external urethral sphincter. Inhibitory amino acids (γ-aminobutyric acid and glycine) and opioid peptides (enkephalins) exert a tonic inhibitory control in the pontine micturition center and regulate bladder capacity. These substances also have inhibitory actions in the spinal cord. Drugs used in management of the bladder symptoms have mainly developed in accordance with this neurochemistry.[3,4] Although antimuscarinics are the mainstay of

TABLE 29-1 ■ Storage and Voiding Symptoms

Storage symptoms	Voiding symptoms
Urgency	Hesitancy
Daytime frequency	Poor flow
Nocturia	Intermittent flow
	Straining
	Incomplete voiding

therapy, other agents have been developed that influence the vanilloid, cannabinoid, and β3 receptors, which are discussed below in the section on treatment.

NEUROGENIC BLADDER DYSFUNCTION

Lower urinary tract symptoms usually consist of problems with storage or problems with voiding (Table 29-1). The pattern of bladder dysfunction following neurologic disease depends to a large extent upon the level of the lesion.[2] The storage function of the bladder is affected following suprapontine or lesions below the pons but above the sacral spinal cord (Table 29-2) resulting in involuntary, spontaneous, or induced contractions of the detrusor muscle (detrusor overactivity), which can be identified during the filling phase of urodynamic testing. This voiding function can be affected by infrapontine lesions. Following spinal cord damage interrupting the connections between sacral and pontine centers, detrusor–sphincter dyssynergia may also occur, resulting in incomplete bladder emptying and abnormally high bladder pressures. With lesions of the conus medullaris, cauda equina, or peripheral nerves, voiding dysfunction predominates and results in poor-detrusor contraction and nonrelaxing urethral sphincters.

Cerebral Lesions

Disorders affecting the cortex or subcortical white matter often result in lower urinary tract symptoms. This occurs most commonly with lesions of the anteromedial frontal lobe, including the anterior part of the cingulate gyrus. The clinical picture is one of severe urgency and frequency of micturition with urge incontinence; the patient is usually socially aware and embarrassed by the incontinence. Urinary retention also has been described but is less common; a small number of patients have been described with urinary retention that resolved with treatment of the frontal lobe disorder.

Urinary incontinence may follow stroke, often with more anteriorly placed infarcts. It has not been possible to demonstrate a correlation between any specific lesion site and the urodynamic findings. The most common cystometric finding is that of detrusor overactivity, and voiding is usually well-coordinated. Patients with hemorrhagic stroke are more likely to have detrusor underactivity. Urinary incontinence at 7 days after stroke is predictive of poor survival, disability, and institutionalization independent of the patient's level of consciousness.

Small-vessel disease of the white matter (leukoaraiosis) has been associated with urgency incontinence as well as falls and cognitive disturbance, especially when it involves the frontal lobes. This may be an important cause of incontinence in functionally independent elderly.

A much less common cause of frontal involvement with urinary incontinence is normal-pressure

TABLE 29-2 ■ Results of the Diagnostic Evaluation for Patients with Suspected Neurogenic Bladder Dysfunction

	Suprapontine lesion, e.g., stroke, Parkinson disease	Infrapontine-suprasacral lesion, e.g., spinal cord injury, multiple sclerosis	Infrasacral lesion, e.g., conus medullaris tumor, cauda equina syndrome, peripheral neuropathy
History/bladder diary	Urgency, frequency, urgency incontinence	Urgency, frequency, urgency incontinence, hesitancy, interrupted stream	Hesitancy, interrupted stream
Postvoid residual (PVR) urine	PVR < 100 ml	±Elevated PVR	PVR > 100 ml
Uroflowmetry	Normal flow	Interrupted flow	Poor/absent flow
Urodynamics	Detrusor overactivity	Detrusor overactivity, detrusor–sphincter dyssynergia	Detrusor underactivity, sphincter insufficiency

hydrocephalus, where incontinence is a cardinal feature. Improvement in urodynamic function has been demonstrated in some patients within hours of lumbar puncture or shunting procedures.

The cause of urinary incontinence in patients with dementia is probably multifactorial, but frontal lobe degeneration probably plays a role. In a study of patients with progressive cognitive decline, incontinence was observed to not occur until more advanced stages of Alzheimer disease but occurred earlier in the course of dementia with Lewy bodies.

Basal Ganglia Lesions

PARKINSON DISEASE

Lower urinary tract symptoms are reported in 38 to 71 percent of patients with Parkinson disease (PD). Storage symptoms are the most common problem, seen in more than 60 percent of these patients, with considerable impact on quality of life. Nocturia is the most common symptom followed by urinary urgency; these are among the most common nonmotor symptoms of PD. Urodynamic studies typically show detrusor overactivity, probably due to neuronal loss in the substantia nigra disinhibiting the normal effect of the basal ganglia on the micturition reflex. Dopamine receptor stimulation through D1 receptors provides the main inhibitory influence on the micturition reflex normally, although dopaminergic stimulation in PD has little apparent impact.

Overactive bladder is common in patients with PD, and many patients have nocturnal polyuria. Patients may also report voiding difficulties and bradykinesia of the pelvic floor muscles resulting in pseudo-dyssynergia. Lower urinary tract symptoms may be multifactorial and other non-neurogenic factors such as prostatic enlargement may contribute. Other medical comorbidities such as diabetes mellitus, congestive cardiac failure, medications (such as diuretics), cerebrovascular disease, and cervical spondylosis may also play a role. Sleep disturbances and disturbed circadian rhythm, which are common in PD, may be closely associated with nocturia.[5]

MULTIPLE SYSTEM ATROPHY

Patients with parkinsonism and early and prominent urogenital complaints may have multiple system atrophy (MSA). Around 40 percent of these patients first present with lower urinary tract symptoms and 97 percent will experience these symptoms during the disease course. Urologic presentations include daytime frequency (about 45%), nocturnal frequency (nearly 70%), urinary urgency (60%), and urge incontinence (66 to 75%).

Bladder symptoms occur much earlier and are more disabling in MSA than PD. Although urgency and frequency occur in both conditions, patients with MSA are more likely than those with PD to have a high (>100 ml) postvoid residual volume, detrusor–sphincter dyssynergia, an open bladder neck at the start of bladder filling on videocystometrogram, and evidence of neurogenic changes on electromyography of the anal sphincter.

Brainstem Lesions

Although the pontine micturition center is essential for micturition, the rarity of brainstem lesions in clinical practice makes it less common to encounter bladder dysfunction secondary to brainstem lesions. In cases with brainstem tumors or other mass lesions, the clinical picture is usually dominated by other long tract and ocular features. Due to the proximity of the pontine micturition center to the medial longitudinal fasciculus, internuclear ophthalmoplegia is a common accompanying finding. Voiding difficulty is a rare but well-recognized symptom of a posterior fossa tumor. When urinary symptoms occur with brainstem stroke, lesions are usually situated dorsally. Brainstem involvement in multiple sclerosis is discussed separately.

Spinal Cord Lesions

The spinobulbar reflex arc is crucial in the control of bladder function in health. Following spinal cord lesions, interruption of this reflex, along with loss of supraspinal control, results in a local spinal reflex that drives bladder contractions. The localization of lesions can be guided by the type of bladder dysfunction observed.

The overactive neurogenic (spastic) bladder occurs following lesions that interrupt the connections between the pontine micturition center and sacral cord micturition centers. Commonly these myelopathic conditions cause quadriplegia or paraplegia. Clinically, patients present with detrusor contraction during bladder filling leading to detrusor overactivity, characterized by urinary frequency, urgency, urge incontinence, and inability to initiate micturition voluntarily. Bladder capacity is reduced, although residual urine may be increased. On examination, the bulbocavernosus and anal reflexes are preserved.

Autonomous neurogenic bladder (detrusor areflexia) may occur with complete lesions below the T12 segment that involve the conus medullaris and cauda equina. Common pathologies include sacral myelomeningocele and tumors of the conus medullaris and cauda equina. This type of neurogenic bladder also occurs during the initial shock phase following spinal cord injury; gradually over the course of weeks new reflexes emerge to drive bladder emptying and cause detrusor contractions in response to low filling volumes. The tone of the detrusor muscle is abolished, there is no awareness of fullness, and the clinical presentation is urinary retention. Overflow incontinence and increased residual urine develop later. On examination, associated saddle anesthesia with absence of the bulbocavernosus and superficial anal reflexes are common. Anal sphincter control is often affected similarly.

Motor paralytic bladder results from lesions involving the efferent motor fibers to the detrusor or the detrusor motor neurons in the sacral spinal cord. Common pathologies include lumbar spinal stenosis, lumbosacral meningomyelocele, or following abdominoperineal resection or radical hysterectomy. Clinically painful urinary retention or impaired bladder emptying is the presenting feature, and residual urine is markedly increased. The bulbocavernosus and superficial anal reflexes are usually absent, but sacral and bladder sensation are preserved.

Sensory paralytic bladder is caused by impairment of the afferent pathways innervating the bladder or by dysfunction of the posterior columns or lateral spinothalamic tract in the spinal cord. Classically, this condition has been described in tabes dorsalis, syringomyelia, and diabetes mellitus. Voluntary initiation of micturition may be retained. On examination, the bulbocavernosus and superficial anal reflexes are variably absent, decreased, or present.

This classification system does not often reflect clinical practice and deviations from these descriptions commonly occur. Following spinal cord injury, the stage of spinal shock is quite variable in presentation. The neurophysiology of recovery from spinal shock has been characterized mainly in cats where, following injury, dormant C fibers emerge as the major afferents, and a spinal segmental reflex is established that results in automatic voiding. The abnormally overactive, small-capacity bladder that characterizes spinal cord disease results in a clinical phenotype characterized by urinary urgency, frequency, and incontinence; however, patients with complete transection of the cord may not complain of urgency.

Bladder Dysfunction in Multiple Sclerosis

Lower urinary tract dysfunction can be one of the main features of multiple sclerosis. Urinary incontinence impacts quality of life for patients and is associated with considerable costs. Up to 75 percent of patients with multiple sclerosis have lower urinary tract symptoms, and overactive bladder and dyssynergia are the most common presentations. Urinary tract infections are common; infection is found in 30 percent of those reporting urinary symptoms. The incidence of lower urinary tract symptoms increases with lower extremity weakness from corticospinal tract dysfunction (usually from spinal cord involvement) and longer disease duration. As the neurologic condition progresses, lower urinary tract dysfunction may become more difficult to treat.

The most common urinary symptom in these patients is urgency, and detrusor overactivity is often seen on urodynamic testing. Patients sometimes initially report hesitancy, but those with more severe symptoms may be unable to initiate micturition voluntarily, emptying their bladders only through involuntary overactive contractions followed by interrupted urinary flow. Evidence of incomplete emptying may come from the need to pass urine again within 5 to 10 minutes (double voiding).

Multiple sclerosis is a dynamic disease, and symptoms may appear or worsen during a relapse and then remit or improve with neurologic remissions. Neurologic symptoms may deteriorate acutely when the patient has an infection, including that of the urinary tract. As the disease progresses, recurrent infections may result in the accumulation of deficits.[6]

Disturbances of Peripheral Innervation

Peripheral neuropathies may result in autonomic symptoms including bladder dysfunction.

DIABETIC NEUROPATHY

Lower urinary tract symptoms are common, although often asymptomatic, in patients with diabetes. Bladder dysfunction is generally accompanied by other symptoms and signs of a generalized neuropathy. The onset of the bladder dysfunction is insidious, with progressive loss of bladder sensation and impairment of bladder emptying over years, finally leading to chronic low-pressure urinary retention. Urodynamic studies demonstrate impaired detrusor contractility, reduced urine flow, increased postmicturition residual volume, and reduced bladder sensation. It seems likely that both afferent and efferent fibers of the local spinal reflex arc are involved, causing reduced awareness of bladder filling and decreased contractility.

Amyloid Neuropathy

Lower urinary tract symptoms generally appear early in the course of amyloid neuropathy and are present in 50 percent of patients within the first 3 years of the disease. Patients most often complain of difficulty in bladder emptying and incontinence, although bladder dysfunction may be asymptomatic. Urodynamic studies have demonstrated reduced bladder sensations, underactive detrusor, poor-urinary flow, and inappropriate opening of the bladder neck. Bladder wall thickening may be seen on ultrasound. Up to 10 percent of patients with familial amyloid neuropathy type I may proceed to end-stage renal disease, often reporting polyuria as an early symptom. Patients with specific mutations may be treated with liver transplantation, and the presence of postoperative urinary incontinence is associated with a higher post-transplant mortality.

Immune-Mediated Neuropathies

Traditionally immune-mediated neuropathies have not been associated with bladder dysfunction. However, many patients with Guillain–Barré syndrome (as high as 25%) report bladder symptoms; these symptoms are more common with more severe neuropathies, appearing after limb weakness is established. Both detrusor areflexia and bladder overactivity have been described. Long-term complications are unusual, and recovery of lower urinary tract symptoms follows the course of the neuropathy.

Autoimmune Autonomic Ganglionopathy

Bladder dysfunction is well-recognized in patients with autoimmune autonomic ganglionopathy. The usual presentation is that of the rapid onset of severe autonomic failure, with orthostatic hypotension, gastrointestinal dysmotility, anhidrosis, erectile dysfunction, and sicca symptoms, often with ganglionic acetylcholine receptor (AChR) antibodies. Bladder dysfunction generally manifests as voiding difficulty and incomplete emptying. The severity and distribution of autonomic dysfunction appear to depend upon the level of antibody titers.

Pure Autonomic Failure

Pure autonomic failure is a synucleinopathy affecting the postganglionic fibers and may mimic MSA. Lewy body deposition is confined primarily to the autonomic ganglia. Nocturia and voiding dysfunction are common, and bladder emptying is often affected.

Myotonic Dystrophy

Although myotonic activity has not been found in either the sphincter or pelvic floor of patients with myotonic dystrophy, bladder symptoms may be prominent and difficult to treat, presumably because bladder smooth muscle is affected. With advancing disease, megacolon and fecal incontinence also may become intractable problems.

Urinary Retention

Urinary retention occurring in isolation is most often due to a urologic cause. However, in some cases a neurologic cause is responsible.[2,4] The differential diagnosis that should be considered once a structural urologic lesion is excluded is found in Table 29-3.

Fowler Syndrome

Urinary retention or symptoms of obstructed voiding in young women in the absence of overt neurologic disease have long puzzled urologists and neurologists alike; in the absence of any convincing organic cause, the condition was thought to be functional. A primary disorder of urethral sphincter relaxation (Fowler syndrome) is typically seen in young women postmenarche who present with retention and bladder capacities often exceeding a liter without experiencing expected urgency. Polycystic ovaries are often associated. Electromyography of striated muscle of the urethral sphincter reveals complex repetitive discharges and myotonia-like activity, called decelerating bursts. The urethral pressure profile and urethral sphincter

TABLE 29-3 ■ Differential Diagnosis in a Patient Presenting With Urinary Retention

Lesions of the conus medullaris or cauda equina
Compressive lesions
Trauma
Intervertebral disc prolapse
Tumor
Granuloma
Abscess
Noncompressive lesions
Vascular: infarction, ischemia (arteriovenous malformation)
Inflammation: myelitis, meningitis retention syndrome
Infection: herpes simplex, varicella zoster, cytomegalovirus
Other neurologic conditions
Spina bifida
Multiple system atrophy
Conditions associated with dysautonomia (e.g., pure autonomic failure, autonomic neuropathies)
Miscellaneous causes
Medications (e.g., opiates, anticholinergics, retigabine)
Fowler syndrome
Radical pelvic surgery
Chronic intestinal pseudo-obstruction
Primary detrusor muscle failure
Idiopathic

Modified from Smith MD, Seth JH, Fowler CJ, et al: Urinary retention for the neurologist. Pract Neurol 13:288, 2013.

volume are elevated. Urinary retention is often successfully managed by sacral neuromodulation.

DIAGNOSTIC EVALUATION

History

The history of patients with suspected lower urinary tract dysfunction should address both storage and voiding. Patients with storage dysfunction complain of frequency of micturition, nocturia, urgency, and urge incontinence. Urgency, frequency, and nocturia, with or without incontinence, is called the "overactive bladder syndrome," "urge syndrome," or "urgency-frequency syndrome."[4] Patients experiencing voiding dysfunction report hesitancy for micturition, a slow and interrupted urinary stream, the need to strain to pass urine, and double voiding. The history of voiding dysfunction is often unreliable as patients may be unaware of incomplete bladder emptying; therefore, the history should be supplemented by a bladder scan, as discussed later. Occasionally, these patients with voiding dysfunction may experience complete urinary retention.

The pattern of lower urinary tract dysfunction is influenced by the site of the neurologic lesion (Table 29-2), and variation from this expected pattern warrants a search for additional problems such as urologic disease.

Bladder Diary

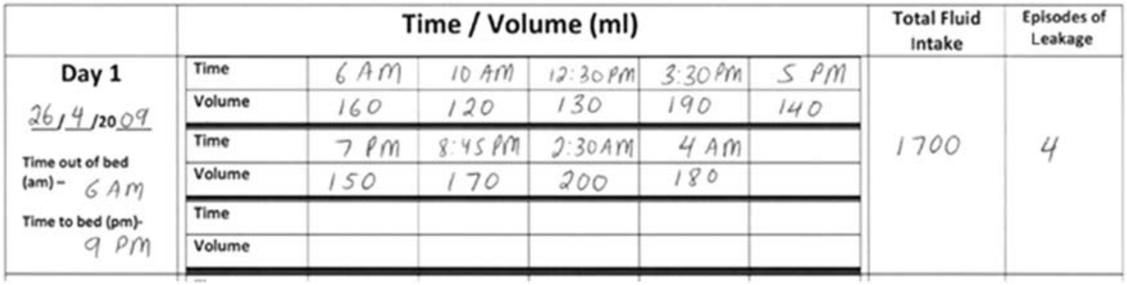
A bladder diary provides a real-time assessment of bladder symptoms and is considered an extension of the history. It provides an opportunity to record the frequency of micturition, volumes voided, episodes of incontinence, and fluid intake over the course of a few days and should be a part of any evaluation of suspected lower urinary tract dysfunction (Fig. 29-2).

Physical Examination

In patients without an established diagnosis, the neurologic examination helps guide whether urologic complaints are neurologic in origin. Bradykinesia or rigidity can point to basal ganglia disorders. Cerebellar ataxia, parkinsonism, and symptomatic postural hypotension should raise the suspicion of MSA. Other autonomic features such as erectile dysfunction, orthostatic hypotension, and constipation may suggest autonomic failure. The findings of saddle anesthesia and absent sacral reflexes (anal or bulbocavernous) point to a lesion of the conus medullaris or cauda equina. The lumbosacral spine should be examined for dimples, tufts of hair, nevi, or sinus, which can be signs of occult spina bifida.

If the neurologic examination is normal in a patient reporting only bladder dysfunction, more detailed investigations such as neuroimaging or physiologic testing are unlikely to reveal an underlying neurologic cause.

In the general physical examination, palpating the abdomen for an enlarged bladder may suggest upper urinary tract damage including stones; tenderness over the loins may occur as well. Digital rectal examination helps to evaluate for prostate enlargement.



	Time / Volume (ml)						Total Fluid Intake	Episodes of Leakage
Day 1 26/4/2009 Time out of bed (am) – 6 AM Time to bed (pm)- 9 PM	Time	6 AM	10 AM	12:30 PM	3:30 PM	5 PM	1700	4
	Volume	160	120	130	190	140		
	Time	7 PM	8:45 PM	2:30 AM	4 AM			
	Volume	150	170	200	180			
	Time							
	Volume							

FIGURE 29-2 ■ Bladder diary recorded over 24 h demonstrating increased daytime and nocturnal urinary frequency, low voided volumes, and incontinence. These findings are seen in patients with detrusor overactivity. (From Panicker JN, Kalsi V, de Seze M: Approach and evaluation of neurogenic bladder dysfunction. p. 61. In Fowler CJ, Panicker JN, Emmanuel A (eds): Pelvic Organ Dysfunction in Neurological Disease: Clinical Management and Rehabilitation. Cambridge University Press, Cambridge, 2010, with permission.)

INVESTIGATIONS

Bladder Scan

Estimating the postvoid residual of urine is an essential step in the investigation of a neurogenic bladder. This assessment is most commonly carried out with a portable bladder scanner or by "in—out" catheterization, especially in patients who perform intermittent self-catheterization. A single measurement of a postvoid residual may not be reliable, and therefore a series of measurements should be made over the course of 1 or 2 weeks.

Screening for Urinary Tract Infections

All patients with lower urinary tract symptoms should be screened for urinary tract infection. Combined rapid tests of urine using reagent strips ("dipstick" tests) have a negative predictive value of 98 percent. However, since the positive predictive value is only 50 percent, a positive test should be followed by a urine culture to confirm infection.

Ultrasound Scan

In patients known to be at risk of upper urinary tract disease, surveillance ultrasonography should be performed periodically to evaluate for upper urinary tract dilatation or renal scarring. Ultrasound may also detect complications of neurogenic bladder dysfunction such as bladder stones.

Urodynamic Studies

Urodynamic studies include measurements of urine flow rate and residual volume, cystometry during both filling and voiding, videocystometry, and urethral pressure profilometry.[7] The term "urodynamics" is often used incorrectly as a synonym for cystometry. From the patient's point of view, urodynamic studies can be divided into noninvasive tests and those tests requiring urethral catheterization.

NONINVASIVE BLADDER INVESTIGATIONS

Uroflowmetry is a valuable test that assesses voiding function. The urinary flow is calculated through a flow meter, usually fitted in a commode or urinal, based upon the power necessary to maintain a rotation speed. A graphic printout of the urinary flow is obtained and time taken to reach maximum flow, maximum and average flow rates, and the voided volume are analyzed (Fig. 29-3). It is important that the patient performs the test with a comfortably full bladder, preferably voiding volumes of at least 150 ml; privacy is essential and a spurious result may be obtained if the patient is not fully relaxed. The test usually complements a bladder scan, and significant outflow obstruction is unlikely if uroflowmetry demonstrates a normal urine flow rate with no significant postvoid residual in the bladder scan.

INVESTIGATIONS REQUIRING CATHETERIZATION

Cystometry assesses changes in the bladder during nonphysiologic filling and also the pressure—flow relationship during voiding. The detrusor pressure is derived by subtraction of the abdominal pressure (measured from a pressure transducer attached to a catheter inserted into the rectum) from the intravesical pressure (measured from a pressure transducer attached to a catheter inserted into the bladder). The rate of filling is recorded by a machine that pumps

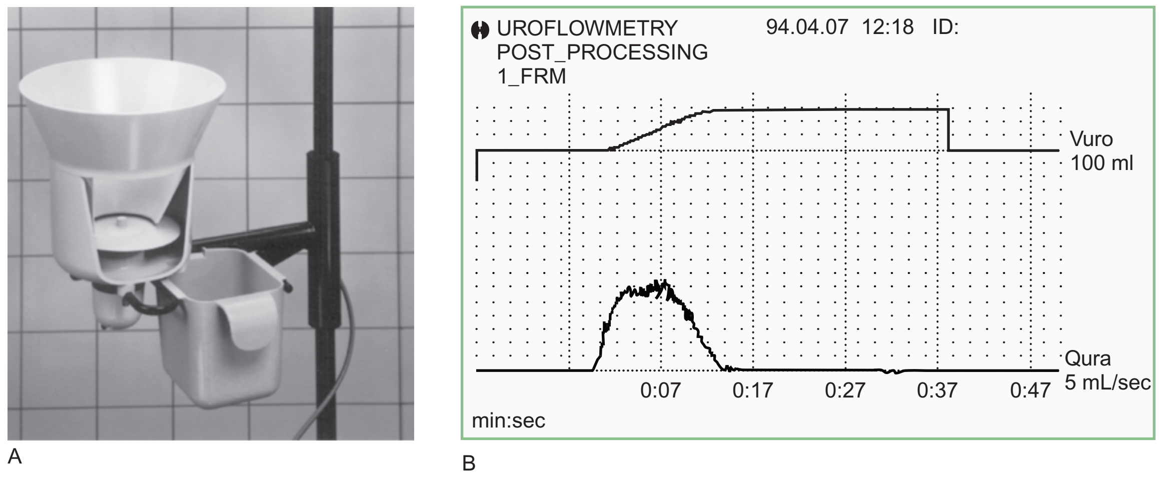


FIGURE 29-3 ■ *A*, Urinary flow meter. The side of the uroflow transducer has been cut away to show the disc at the base of the funnel, which rotates as urine passes into the collecting vessel. *B*, A normal printout from the uroflowmeter. A total of 290 ml was voided *(upper trace)*, with a maximum flow rate of 30 ml per sec *(lower trace)*. (From Dantec Medical A/S, Copenhagen, with permission.)

sterile water or saline through the catheter into the bladder. For speed and convenience, most laboratories use filling rates of between 50 and 100 ml per minute. This nonphysiologic rapid filling means that the full bladder capacity can be reached usually within 7 or 8 minutes. First sensation of bladder filling may be reported at around 100 ml, and full capacity is reached between 400 and 600 ml. In healthy subjects with a "stable" bladder, the bladder expands to contain this amount of fluid without an increase of pressure above 15 cmH_2O. The main abnormality sought during filling cystometry in patients with a neurologic disease is the presence of detrusor overactivity (Fig. 29-4) characterized by involuntary detrusor contractions which may be spontaneous or provoked. Detrusor overactivity of neurogenic origin is indistinguishable from other causes of detrusor overactivity on urodynamic testing. When bladder filling has been completed, the patient voids into the flow meter with the bladder and rectal lines still in place as valuable information can be obtained by measuring detrusor pressure and urine flow simultaneously.

Cystometry may be valuable in demonstrating the underlying pathophysiology of the lower urinary tract and may identify concomitant urologic conditions such as bladder outflow obstruction or stress incontinence. A general criticism is that findings on cystometry contribute little to elucidating the underlying disorder. In many patients with a neurogenic bladder, the "urodynamic diagnosis" does not influence management, and the need to perform a complete urodynamic study in all patients with a suspected neurogenic bladder is therefore unclear. The decision to carry out cystometry should include consideration of the underlying neurologic diagnosis, the perceived risk of upper tract damage, and sometimes, response to initial treatment. Patients with spinal cord injury, spina bifida, and possibly advanced multiple sclerosis should undergo urodynamic studies as part of the initial evaluation as they are at higher risk of upper tract involvement and renal impairment (although ultrasound is a less invasive method for monitoring the upper tract). In other conditions such as early multiple sclerosis, stroke, and PD, the risk for developing upper urinary tract damage is less, and the initial evaluation may be restricted to noninvasive tests; cystometry is indicated when bladder symptoms are unclear or in patients responding inadequately to first-line management.

Videocystometry

Videocystometry is cystometry carried out using a contrast-filling medium visualized radiographically. Urologists and urogynecologists have found videocystometry useful in detecting sphincter or bladder neck incompetence in patients with stress incontinence. The technique also gives additional information regarding morphologic changes that may occur as a consequence of neurogenic bladder dysfunction, including the presence of vesicoureteric reflux. The opportunity to inspect the outflow tract

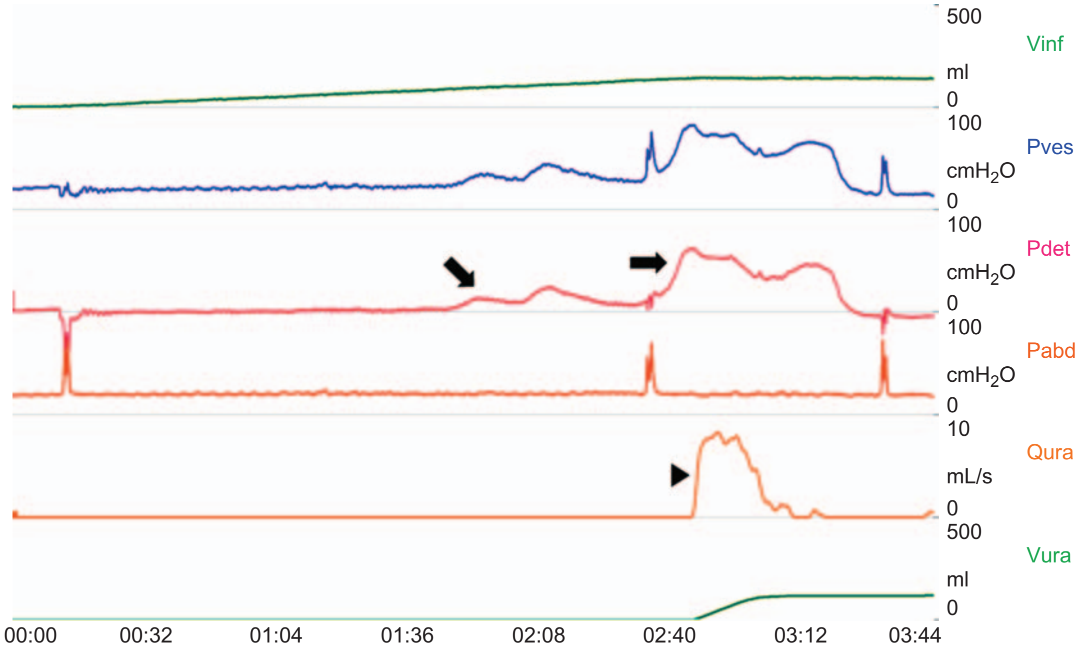


FIGURE 29-4 ■ Filling cystometry demonstrating detrusor overactivity. The dark orange line (Pabd) is the intra-abdominal pressure recorded by the rectal catheter, the dark blue line (Pves) is the intravesical pressure recorded by the bladder catheter. The pink line (Pdet) is the subtracted detrusor pressure (Pves − Pabd). Green lines represent volume infused during the test (Vinf) and volume voided (Vura), while the orange line represents urinary flow (Qura). The black arrows demonstrate detrusor overactivity and the black arrowhead indicates associated incontinence. (From Panicker JN, Fowler CJ: The bare essentials: uro-neurology. Pract Neurol 10:178, 2010, with permission.)

during voiding is of great value in patients with suspected obstruction.

Pelvic Neurophysiology

Various neurophysiologic investigations of the pelvic floor have been developed for assessing the innervation of muscles that are difficult to test clinically. Their clinical utility has been debated, and they currently play a role only in the assessment of patients presenting in specific clinical situations.

ELECTROMYOGRAPHY

Pelvic floor electromyography was first introduced with the aim of recognizing detrusor–sphincter dyssynergia, but it is currently performed only rarely. Technically the best signal is obtained using a needle electrode, but the discomfort from the needle itself can impair normal relaxation of the pelvic floor. Surface recording electrodes have been used, but they may record a considerable amount of noise artifact, which makes interpretation difficult. The value of the information provided is limited, and the demonstration of detrusor–sphincter dyssynergia is most often achieved by less invasive techniques such as videourodynamics.

Concentric needle electromyography of the pelvic floor is possible since motor units of the pelvic floor and sphincters fire tonically; they therefore may be captured conveniently using a trigger and delay line and subjected to individual motor unit analysis. Well-established normative values exist for the normal duration and amplitude of motor units recorded from these sphincter muscles.

Sphincter Electromyography for Suspected Cauda Equina Lesions

Lesions of the cauda equina are an important cause of pelvic floor dysfunction. Although electromyography may demonstrate pathologic spontaneous activity 3 weeks or more after injury, these changes of denervation often become lost in the tonically firing motor units of the sphincter. Most often with long-standing cauda equina syndrome, electromyography of the external anal sphincter demonstrates changes of chronic reinnervation, with a reduced interference pattern and enlarged motor units (>1 mV amplitude) along with polyphasic potentials.

Sphincter Electromyography in Multiple System Atrophy

Postmortem studies of MSA have demonstrated a selective loss of anterior horn cells in Onuf nuclei, which are spared in PD. This finding may explain the early urinary symptoms and sphincter involvement in MSA. Sacral cord involvement may precede central changes responsible for lower urinary tract symptoms in these patients. The central pathology of MSA may explain the symptoms of overactive bladder that may occur. The Onuf nucleus involvement may account for the abnormalities seen in the external urethral sphincter. These changes can be detected easily using electromyography (Fig. 29-5). There is debate on the role of anal sphincter electromyography in the diagnosis of MSA.

Sphincter Electromyography for Urinary Retention in Young Women

A characteristic abnormality in isolated urinary retention in young women can be found on urethral sphincter electromyography; complex repetitive discharges, akin to the sound of "helicopters" along with decelerating bursts, a signal somewhat like myotonia and akin to the sound of "underwater recording of whales," can be found. It has been proposed that this abnormal spontaneous activity results in an impairment of relaxation of the urethral sphincter, which may cause urinary retention in some women and obstructed voiding in others. This condition, known as Fowler syndrome (see above), is also characterized by elevated urethral pressures.

Penilo-Cavernosus (Bulbocavernosus) Reflex

The penilo-cavernosus reflex, formally known as the "bulbocavernosus" reflex, assesses the sacral root afferent and efferent pathways. The dorsal nerve of the penis (or clitoris) is electrically stimulated and recordings are made from the bulbocavernosus muscle, usually with a concentric needle. This test may be of value in patients with bladder dysfunction suspected to be secondary to cauda equina or lower motor neuron pathway damage. A normal response does not completely exclude the possibility of an axonal lesion.

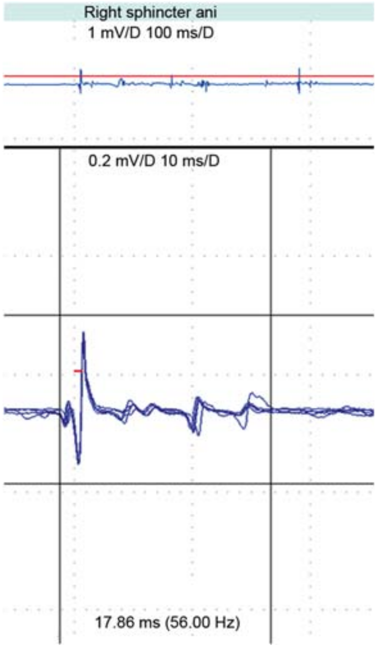


FIGURE 29-5 ■ Concentric needle electromyogram of the external anal sphincter from a 64-year-old man presenting with parkinsonism and urinary retention. Duration of the motor unit is 17.9 msec (normal <10 msec) with a mean duration of all the motor units recorded during the study of 22.9 msec; these prolonged motor units suggest chronic reinnervation and are compatible with a diagnosis of multiple system atrophy.

Pudendal Nerve Terminal Motor Latency

The only test of motor conduction for the pelvic floor is the pudendal nerve terminal motor latency. The response is obtained by stimulating the pudendal nerve either rectally or vaginally, adjacent to the ischial spine using a finger-mounted stimulating device with a recording electrode around the base of the finger that records from the external anal sphincter. Prolongation suggests pudendal nerve damage. However, as a prolonged latency is a relatively poor marker of denervation, the test has not proved contributory in the investigation of patients with suspected pudendal neuralgia.

PUDENDAL SOMATOSENSORY EVOKED POTENTIALS

Pudendal somatosensory evoked potentials can be recorded from the scalp following electrical stimulation of the dorsal nerve of the penis or clitoris. Although abnormal when a spinal cord lesion is the cause of sacral sensory loss or neurogenic detrusor overactivity, such pathology is usually apparent from the clinical examination. The latencies of the evoked potentials recorded are compared to those found with stimulation of the posterior tibial nerve.

COMPLICATIONS OF NEUROGENIC BLADDER DYSFUNCTION

Detrusor overactivity and reduced bladder wall compliance may lead to raised intravesical pressure, which can, in turn, lead to structural changes in the bladder wall such as trabeculations and diverticuli. The upper urinary tract (kidney and ureter) can also be affected through the vesicoureteric reflux, resulting in hydronephrosis along with renal impairment and possible failure. For reasons that are unclear, upper urinary tract damage and renal failure are less common in multiple sclerosis than in traumatic spinal cord injury or spina bifida. The risk of upper urinary tract damage is highest in patients who have raised intravesical pressure due to detrusor overactivity, low bladder compliance, and a competent bladder neck. Patients with a neurogenic bladder are prone to genitourinary tract infections such as cystitis, pyelonephritis, and epididymo-orchitis as well as bladder stones.

MANAGEMENT OF NEUROGENIC BLADDER DYSFUNCTION

The goals of managing neurogenic bladder dysfunction are to achieve urinary continence, prevent urinary tract infections, and preserve upper urinary tract function, all of which may improve the quality of life of patients with neurologic disease. The management of neurogenic bladder dysfunction must address both voiding and storage dysfunction (Fig. 29-6).

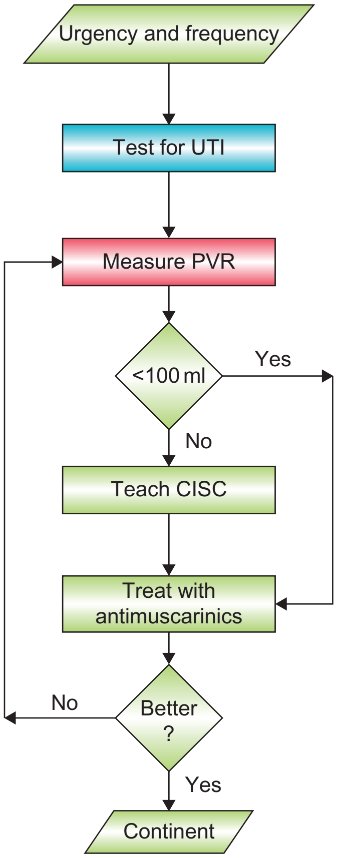


FIGURE 29-6 ■ Algorithm for the management of neurogenic lower urinary tract dysfunction. CISC, clean intermittent self-catheterization; PVR, postvoid residual urine; UTI, urinary tract infection. (From Fowler CJ, Panicker JN, Drake M, et al: A UK consensus on the management of the bladder in multiple sclerosis. J Neurol Neurosurg Psychiatry 80:470, 2009, with permission.)

Management of Voiding Dysfunction

A postvoid residual volume of more than 100 ml, or more than one-third of bladder capacity, is considered incomplete emptying. This voiding dysfunction can exacerbate detrusor overactivity, and an overactive bladder constantly stimulated by a residual volume responds with contraction, producing symptoms of urgency and frequency, making antimuscarinic medications less effective.

The widespread use of intermittent self-catheterization has greatly improved the management of neurogenic bladder dysfunction. There is no consensus regarding the amount of residual volume at which intermittent self-catheterization should be initiated. Sterile intermittent catheterization was previously the standard, but a clean, rather than sterile, technique has been found to be adequate. Intermittent catheterization is best performed by the patient, who should be taught by an experienced provider such as a nurse continence advisor. Neurologic lesions affecting manual dexterity, visual acuity, or cognitive function may require the patient to be assisted by a partner or other provider. The incidence of symptomatic urinary tract infections is low when catheterization is performed regularly.

α-Blockers can relax the internal urethral sphincter in men, and although they improve bladder emptying and reduce postvoid residual volumes, their use is usually not recommended unless concomitant prostatic enlargement is present. Botulinum toxin injections into the external urethral sphincter may improve bladder emptying in patients with spinal cord injury and significant voiding dysfunction. Suprapubic vibration using a mechanical "buzzer" is modestly effective in patients with multiple sclerosis who have incomplete bladder emptying and detrusor overactivity. The Credé maneuver (pressure applied from the umbilicus toward the pubis) and reflex voiding using nonforceful trigger techniques are usually not recommended as they may result in high detrusor pressure and incomplete bladder emptying during voiding.

Management of Storage Dysfunction

GENERAL MEASURES

Nonpharmacologic strategies are useful in the early stages of storage dysfunction when symptoms are mild. A restriction of fluid intake to around 1 to 2 liters daily is suggested, and it is often helpful to assess fluid balance by means of a bladder diary. Reduction of caffeine intake may reduce urgency and frequency, especially in patients who drink coffee or tea excessively. Bladder retraining, whereby patients void at regular timed intervals and then voluntarily "hold on" for increasingly longer periods of time, aims to restore the normal pattern of micturition. Pelvic floor exercises and neuromuscular stimulation may also be useful, once voiding dysfunction has been excluded, in the symptomatic treatment of an overactive bladder.[8]

ANTIMUSCARINIC MEDICATIONS

Detrusor overactivity is a major cause of incontinence in patients with neurogenic bladder disorders. The first-line treatment of detrusor overactivity is with antimuscarinic drugs, but the evidence for their efficacy is limited. A systematic review found no significant difference in efficacy between the various antimuscarinic drugs in patients with neurogenic bladder.[9] Oxybutinin was one of the earlier drugs introduced, but propiverine, trospium, propantheline, and tolterodine have all been shown to produce clinical and some urodynamic improvement in detrusor overactivity. Adverse events are due to nonspecific anticholinergic actions and include dry mouth, blurred vision for near objects, tachycardia, and constipation. These drugs can also block central muscarinic receptors and cause impairment of cognition and consciousness. Medications that have low selectivity for the M1 receptor, such as darifenacin, or restricted permeability across the blood–brain barrier, such as trospium, are probably less likely to cause cognitive disturbances which may be relevant in specific patient groups like PD.[10] The postvoid residual urine volume may increase following treatment and should be monitored by serial bladder scans. Many patients also have underlying voiding dysfunction, and it is often judicious to use antimuscarinic medications along with clean intermittent self-catheterization.

BETA-3 RECEPTOR AGONISTS

Mirabegron is a $\beta 3$ receptor agonist that has been approved for use in patients with neurogenic bladder symptoms. The advantage is that it does not have the antimuscarinic side effects. Common side effects include palpitations and increased blood pressure, so it is best to screen patients for cardiac risk factors before prescribing.[11]

DESMOPRESSIN

Desmopressin, a synthetic analogue of arginine vasopressin, reduces urine production and volume by promoting water reabsorption at the distal collecting tubules of the kidney. The evidence for its efficacy in the treatment of nocturia and daytime frequency in patients with multiple sclerosis suggests that it provides symptom relief for up to 6 hours. Desmopressin is useful also in managing patients with orthostatic hypotension. Side effects include the risk of hyponatremia, particularly in older patients, and it should be prescribed with caution in those with dependent leg edema or congestive heart failure. In patients over 65 years of age who are taking the drug, serum sodium levels should be measured at baseline and again at 3 and 7 days at the beginning of treatment or when the dose is changed.

CANNABINOIDS

Cannabinoids have limited efficacy on urinary disturbances in patients with multiple sclerosis. In one study of orally administered Δ^9-tetrahydrocannabinol extract, frequency, nocturia, and incontinence episodes were diminished. Oral nabiximols have demonstrated a significant reduction in the number of episodes of nocturia and of voids per day, as well as improvement in overall bladder control.

BOTULINUM TOXIN

Botulinum toxin was used initially on the basis that it blocks synaptic release of ACh from parasympathetic nerve endings and produces paralysis of the detrusor muscle along with a demonstrable increase in bladder capacity. Accumulating evidence indicates that the mechanism of action is more complex, however, and may involve afferent bladder innervation as well. Botulinum toxin type A injections of the detrusor muscle under cystoscopic guidance are now approved to manage refractory neurogenic detrusor overactivity in several countries, including the United States. The duration of effect is 9 to 13 months. Two pivotal phase III studies demonstrated that onabotulinumtoxinA significantly improves overactive bladder symptoms, urodynamic parameters, and quality of life, although patients often have to perform clean intermittent self-catheterization afterwards depending on the dose administered (30 to 42% in one study). Evidence also supports the efficacy of detrusor injections of botulinum toxin A in the treatment of neurogenic detrusor overactivity in adults with multiple sclerosis and spinal cord injury.[12] Studies also suggest that patients receiving botulinum toxin injections have fewer urinary tract infections and reduced catheter bypassing (urethral leakage while using an indwelling catheter).

VANILLOIDS

Despite the initial enthusiasm for its use, intravesical vanilloid therapy generally has been superseded by botulinum toxin treatments. Only a few centers worldwide offer resiniferatoxin treatment.

NERVE STIMULATION

Sacral Neuromodulation

An extradural sacral nerve stimulator can be useful in conditions resistant to antimuscarinic medications. The mechanism of action is likely stimulation of pelvic afferents, which are known to have an inhibitory effect on the detrusor. Implanting the stimulator requires evaluation during a test phase to determine whether the patient's symptoms are improved as judged by bladder diaries and measurement of residual volumes. If effective, the battery is implanted in a subcutaneous pocket and connected to the stimulating lead. The stimulator is continuously active, although it can be maintained at a subsensory level. There is only limited evidence supporting sacral neuromodulation in patients with progressive neurologic conditions.

Percutaneous Tibial Nerve Stimulation

Percutaneous tibial nerve stimulation (PTNS) has been found to be effective in neurologic patients reporting overactive bladder symptoms. It does not worsen voiding difficulties or increase the postvoid residual, unlike other treatments such as antimuscarinic agents or botulinum toxin. PTNS is an effective option for managing mild or moderate overactive bladder symptoms, and a typical treatment course consists of stimulating the nerve intermittently for 30 minutes over 12 sessions, typically weekly, through a fine-gauge stainless steel needle using a fixed-frequency, variable current strength electrical signal. Effects are relatively short lived and the need to return for maintenance top-up treatments is influenced by the degree of improvement of lower urinary tract symptoms.[13] Responders to treatment returning for maintenance PTNS more often report improvements in nocturia and perceived benefits over time, compared to those not returning for maintenance treatment.

Transcutaneous tibial nerve stimulation in volves stimulating the nerve using a cutaneous electrode which may be performed at home and has been shown to be safe and effective in patients with MS and stroke patients experiencing urgency incontinence. The advantages of tibial nerve stimulation include that it is noninvasive and has minimal adverse events.

Nerve Root Stimulators

In patients with complete spinal cord transection, but in whom the caudal section of the spinal cord and its roots are intact, implantation of a nerve root stimulator should be considered. Stimulating electrodes are placed around the lower sacral roots (S2 to S4) and activated by an external switching device. The stimulating electrodes are usually applied intrathecally to the anterior roots, and the posterior roots are severed at the same time. After the implant, adjustments are made to stimulation parameters so that the patient obtains maximum benefit in terms of making the bladder contract for voiding, assisting defecation, or producing penile erection. Although such devices are highly effective in selected cases, the additional neurologic deficit caused by the need for sectioning of the dorsal roots and resulting erectile dysfunction has reduced its acceptance. These stimulators are suitable only for patients with complete spinal cord lesions and are not effective in partial cord lesions or chronic neurologic disease.

SURGERY

Various surgical procedures to rectify a disorder causing incontinence in otherwise fit and healthy persons are often highly successful. Even after spinal cord injury, a surgical option might be the best solution for long-term bladder management. These

TABLE 29-4 ■ Situations Prompting Early Referral to a Urologist

- Hematuria
- Renal impairment
- Frequent urinary tract infections
- Suspicion of concomitant urologic pathologies such as bladder outlet obstruction due to prostate enlargement in men or stress incontinence in women
- Symptoms refractory to treatment
- Consideration of suprapubic catheterization
- Consideration of urologic procedures such as intradetrusor injections of botulinum toxin A or surgeries such as augmentation cystoplasty or urinary diversion

procedures are typically not effective in chronic and progressive neurologic conditions such as multiple sclerosis.

PERMANENT INDWELLING CATHETERS

When incontinence is refractory to management or the patient is no longer able to perform self-catheterization, an indwelling catheter may become necessary. The long-term complications of urethral catheters are well-known and include catheter bypassing, which occurs when strong detrusor contractions produce a rapid urine flow that cannot drain sufficiently quickly. A common response to bypassing is to use a wider-caliber catheter, and consequently the bladder closure mechanism becomes progressively stretched and destroyed. Bladder stones and recurrent infections are also more likely in patients with an indwelling catheter.

A preferred alternative to an indwelling urethral catheter is a suprapubic catheter, which can be inserted by a urologist. Extreme care is required since these patients often have small, contracted bladders, contributing to the risk of bowel perforation during placement. A suprapubic catheter is a better long-term alternative to urethral catheters since it preserves urethral integrity and sexual function, while leading to fewer problems with perineal hygiene.

Stepwise Approach to Neurogenic Bladder Dysfunction

The treatment options offered to a patient with lower urinary tract dysfunction should reflect the severity of bladder problems, which generally parallel the extent of neurologic disease. There are specific situations where patients should be seen early by a urology consultant (Table 29-4).

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CHAPTER

30

Sexual Dysfunction in Patients with Neurologic Disorders

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SEXUAL FUNCTION AND THE NERVOUS SYSTEM
- Desire
- Arousal
- Orgasm
- Topographic Anatomy of Nerves in the Pelvis
- Change in Sexual Function With Aging

EVALUATION OF PATIENTS WITH SEXUAL DYSFUNCTION AND NEUROLOGIC DISORDERS
- History
- Clinical Examination
- Investigation of Genital Reaction and Arousal
- Investigations of Neurologic Function
- Hormone Measurement

SEXUAL DYSFUNCTION IN PATIENTS WITH NEUROLOGIC DISEASE
- Head and Brain Injuries
- Cerebrovascular Disease
- Epilepsy
  - *Seizures and Sexual Symptoms*
  - *Interictal Phenomena*
- Parkinson Disease
- Multiple System Atrophy
- Other Extrapyramidal Disorders
- Hypothalamic and Pituitary Disorders
- Multiple Sclerosis
- Lesions of the Spinal Cord
- Cauda Equina Lesions and Lumbar Stenosis
- Spinal Malformations
- Localized Nerve Lesions
- Diabetic Polyneuropathy
- Chronic Renal Failure
- Other Acquired Polyneuropathies
- Hereditary Polyneuropathies
- Amyotrophic Lateral Sclerosis
- Hereditary Neuromuscular Diseases
- Adverse Sexual Reactions to Medications

THERAPY
- Treatment of Neurogenic Erectile Dysfunction
  - *Oral Agents*
  - *Intracavernous Injection Therapy*
  - *Intraurethral Therapy*
  - *Vacuum Devices*
  - *Surgical Treatment*
- Ejaculatory Dysfunction in Men With Neurologic Disorders
- Treatment of Abnormalities of Libido
- Treatment in Women With Sexual Dysfunction

NEUROLOGIC PROBLEMS ASSOCIATED WITH SEXUAL ACTIVITY
- Headache
- Transient Global Amnesia

CONCLUDING COMMENTS

Sexual excitement and satisfaction from adequate stimuli are a normal component of a fulfilled life. The somatic and psychosocial factors involved may be compromised by neurologic disease. Sexual dysfunction may occur as the presenting symptom of a developing neurologic disease (e.g., erectile dysfunction in multiple system atrophy) or as an isolated phenomenon after local nerve injury (e.g., painful clitoral dysesthesia after pudendal nerve lesion), or it may be due to more general effects of a neurologic disorder.

Sexual disorders, such as loss of sexual desire, erectile dysfunction in men, decreased lubrication in women, and disturbances of ejaculation and orgasm, are common in patients with neurologic disorders but are usually not communicated by them to the neurologist. Sexual functioning needs to be addressed because it may be relevant for diagnosis, is a major determinant of quality of life, and may respond to treatment. The focus of this chapter is on the more classic neurologic dimension of sexuality as a physiologic function dependent on the integrity of neural control, on sexual

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dysfunction as a consequence of neurologic disease, and on management of neurologic patients with sexual dysfunction.

SEXUAL FUNCTION AND THE NERVOUS SYSTEM

To the neurologist, sexual behavior involves a series of neurally controlled phenomena occurring in a hormonally defined milieu. Sexuality depends also on psychosocial factors, however, and the perspective of partnership and social issues should not be forgotten.

The sexual response is traditionally conceptualized as consisting of several phases, including desire, excitation, and orgasm. Although it has been criticized as male oriented, it still serves to structure the relevant observational, neuroanatomic, physiologic, and clinical issues for both genders. Differences in sexual behavior between men and women exist and are determined also by biologic factors.

Any lesion involving neural tissue relevant for sexual responses may cause dysfunction, as also may lesions of other neural structures more generally involved in control of sensation, motor function, cognition, and behavior (Fig. 30-1). Thus, all primary sensory areas plus the parietal and inferior temporal lobes process sexual stimuli, the forebrain regulates the initiation and the execution of sexual behavior, the medial preoptic area integrates sensory and hormonal signals, and the amygdala plays a role in the reward aspects of sexual function. Neurons from the paraventricular nucleus project to the thoracic and lumbosacral nuclei concerned with the sexual response, the hypothalamospinal projections being situated in the posterolateral funiculus of the spinal cord. Finally, the sympathetic, parasympathetic, and somatic efferents affect the sexual response, with genital afferents playing a part in the initiation of the cycle and in reinforcing the response. Furthermore, the hypothalamus controls the gonadotropic functions of the pituitary gland and thus prenatal development of genital organs, pubertal development, and the menstrual cycle; hormones finally influence the development of the nervous system.

Fertility and procreation are importantly linked to sexuality, but will not be discussed in depth here.

Desire

Desire or sexual interest (libido) refers to the extent that an individual responds to or seeks out erotic stimuli. This varies with time and circumstances, and its measurement depends on self-ratings of such items as the frequency of spontaneous sexual thoughts, the excitement provoked by them, and the resulting behavioral response. Desire is enhanced by sexual activity itself, exciting circumstances, new sexual partners, hypomania, and certain focal brain lesions (particularly of the frontal and temporal lobes). Depressed patients may develop more than their premorbid levels of sexual desire in response to antidepressant medication, as may patients with Parkinson disease in response to dopaminergic therapy. Sexual interest may be lowered by lack of opportunity, age, malnutrition, certain addictive or sedative drugs, debilitating illness, depression, epilepsy, and certain focal brain lesions.

Animal experiments have revealed dopaminergic-stimulating and serotonergic-inhibiting mechanisms controlling sexual interest. Androgens are necessary for normal libido, although there are some uncertainties related to this issue. In women, sexual desire is also associated with levels of free testosterone.

The rhinencephalon, including the limbic cortex, is important for sexual desire and behavior. The basal hypothalamus is particularly relevant; it is affected by tissue levels of the sex steroid hormones, and lesions involving it may lead to loss of desire. The medial preoptic area is involved in regulating sexual motivation and performance, and dopamine may regulate penile erection at this level. A functional magnetic resonance imaging (fMRI) study of sexual interest in men (by comparing erotic to sport clips) showed activation in the right parieto-occipital sulcus, the left superior occipital gyrus, and the precentral gyri. Functional imaging studies have demonstrated that the ovulatory cycle influences sexual interest and that activations in relevant brain areas are relatively greater in premenopausal than menopausal women.

Arousal

Sexual excitement results from genital stimulation, other sensory stimuli, or sexual ideation. The glans in both genders has a high receptor density: up to 80 to 90 percent of the nerve endings are free in the most superficial layer of mucosa. There are also corpuscular-type endings beneath the mucosal layer.

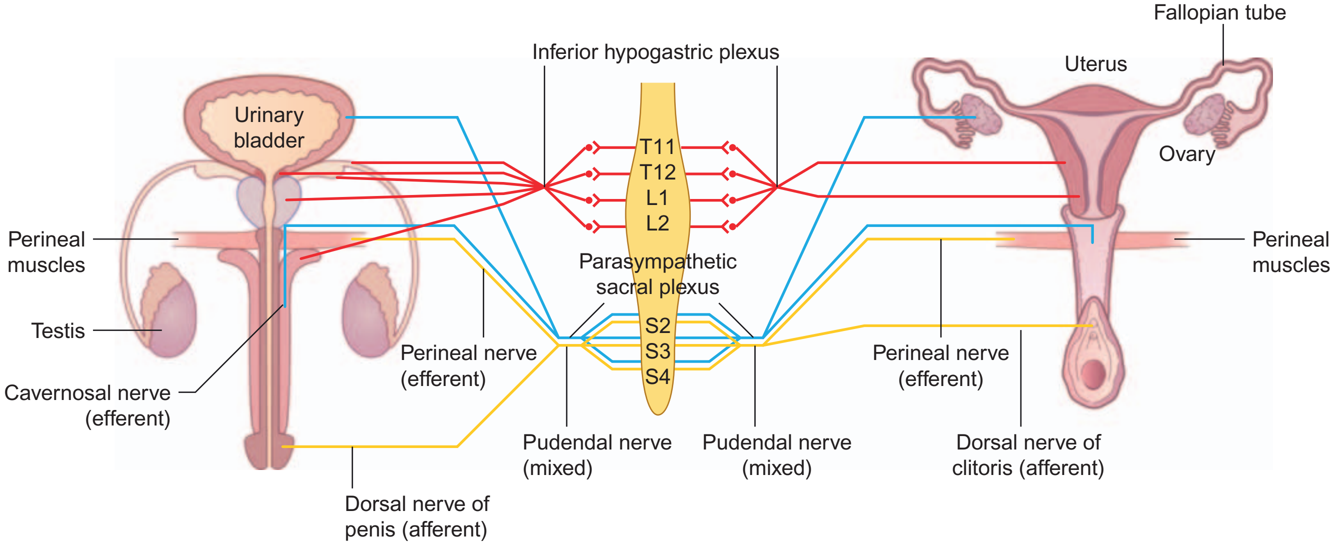
Inferior hypogastric plexus
Fallopian tube
Uterus
Urinary bladder
T11
T12
L1
L2
Ovary
Perineal muscles
Perineal muscles
Parasympathetic sacral plexus
Testis
S2
S3
S4
Perineal nerve (efferent)
Perineal nerve (efferent)
Cavernosal nerve (efferent)
Pudendal nerve (mixed)
Pudendal nerve (mixed)
Dorsal nerve of clitoris (afferent)
Dorsal nerve of penis (afferent)

FIGURE 30-1 ■ Schematic representation of the autonomic and somatic innervation of the male *(left)* and female *(right)* sexual organs.

The receptors are of two types: slowly adapting distally and rapidly adapting proximally, with afferent C and A delta fibers. Surrounding the cavernous bodies are large nerve endings that resemble onions, with thick lamellae and a central nerve fiber connected to thick, myelinated nerve fibers. These nerve endings respond to deep pressure and vigorous movement. Receptors close to the cavernous bodies are influenced by the amount of engorgement of cavernous tissues so that touch may be experienced simply as touch or as a sexual stimulus depending on the degree of engorgement.

Sensory information from the glans and skin of the penis and clitoris is conveyed through bilateral branches of the pudendal nerve (the dorsal nerves of penis/clitoris), as shown schematically in Fig. 30-1. The afferents from the root of the penis (and from the anterior part of the scrotum) join the ilioinguinal nerve. Genital afferents synapse in the spinal cord via interneurons with both somatic and autonomic motor neurons; those afferents destined for supraspinal structures travel in the anterolateral funiculus. “Erotically colored” sensations from the genital region are conveyed by the spinothalamic pathways, and patients with selective damage to these tracts may complain of anorgasmia and ejaculatory failure. Orgasmic sensation is blocked by bilateral anterolateral section of the spinal cord (cordotomy).

Somatic sensory afferents deliver information on tactile sexual stimuli that, after synapsing in the sacral spinal cord, induce local sexual responses (i.e., erectile and glandular responses). Sensory information also passes to suprasacral regions and is operative in other reflex activity, leading to awareness of sexual excitation. Both thalamic and cortical areas receive sensory input from the genitals, and sexual feelings may be elicited when such areas are stimulated. In the primary sensory cortex the genitals are traditionally thought to be represented in the parasagittal area; functional imaging suggests localization on the medial edge of the hemispheric convexity.

Somatosensory input from other body parts (“erogenic zones”) may—subject to somatic and individual psychologic factors and dependent on context—also lead to sexual excitement. Adequate sexual excitation can be achieved by stimuli delivered through cranial nerves. Although such “extrinsic” excitation—similarly to that achieved by stimulation of sexual organs—should also be called reflex (because there may be little “intrinsic” contribution to the excitatory response), it has traditionally been called “psychogenic.” Cortical and subcortical structures related to the limbic system elicit erection when stimulated. (Mental imagery is the “real” psychogenic activator.)

In men during visually evoked sexual arousal, regional cerebral blood-flow measurements by positron emission tomography (PET) have demonstrated activation of the inferior temporal cortex (a visual association region) bilaterally, of the right insula and inferior frontal cortex (regions processing sensory information and motivational state), and the left anterior cingulate cortex (involved in neuroendocrine function).[1] Sexual arousal correlated with the magnitude of hypothalamic activation but was more pronounced in men than women. The occipitotemporal region was more activated in men, and the parietal lobe in women.[2]

Sexual excitement leads to a complex response of the autonomic nervous system, and also to typical posturing in different species; in humans this behavior has been studied little but is understood to be influenced by psychosocial and cultural factors.

Parasympathetic efferents from the S2 to S4 spinal segments, traveling through the sacral plexus and cavernosal nerves, initiate erection (Fig. 30-1). (The male erection has to be firm enough for vaginal penetration, and maintained throughout intercourse to bring about ejaculation, which in turn should deliver sperm to the uterine cervix.)

Blood flow in the penile artery, or the corresponding artery in the clitoris, increases. The smooth muscle of the cavernosal sinuses in the penile corpora relax, and the helicine arterioles branching from cavernosal arteries, selectively shunt blood flow to the lacunar spaces of the cavernosal bodies, filling them with blood. Subtunical venules are compressed so that corporeal venous return is restricted, resulting in increasing intracorporeal pressure. The pressure stabilizes at approximately systolic blood pressure, resulting in penile (and clitoral) tumescence and rigidity. Continued sacral parasympathetic activity maintains this erection.

The nerves of the corpora cavernosa have anatomic characteristics different from other nerves. The intracavernous nerves are located in fibrous tunnels, into which numerous fibrous bundles are attached. Contraction of striated pelvic floor muscles, the ischiocavernous muscles in particular, brought about through pudendal nerve activity, increases the rigidity of erection.

In women, parasympathetic activity causes clitoral erection, engorgement of the labia, and vaginal lubrication. The lubrication during sexual arousal is due to transudation through the vaginal wall. Another source is secretion from paraurethral glands (emptying into the urethra). Increased vaginal blood-flow, lubrication, and erection of cavernous tissue in the clitoris and around the outer part of the vagina are the female homologues of the male erectile response; indeed, lubrication occurs during rapid-eye-movement sleep in women. The response is dependent on innervation and a normal estrogen level.

In the periphery, the main proerectile transmitter is nitric oxide, which is colocalized with vasoactive intestinal peptide and acetylcholine; the main anti-erectile neurotransmitter is norepinephrine. The same mechanisms are responsible for clitoral erection.

Erections can still occur in men and animals after lesions of the sacral cord and pelvic nerves. This is due to the "alternative" proerectile pathway mediated through the hypogastric nerve. This explains the so-called psychogenic erections of paraplegics with conus or cauda equina lesions but preserved thoracolumbar segments. Similarly, women with injury to the sacral spinal cord and an ability to perceive pinprick in the T12 to L2 segments may retain the capacity for psychogenic genital vasocongestion. In women with complete spinal cord injuries and preserved sacral segments, such a response is as a rule obtained only by manual genital stimulation. Thus, the reflex–"psychogenic" dichotomy of the genital sexual response can be seen in both sexes.

Inhibitory influences on the sexual response also exist. In nucleus paragigantocellularis a majority of the serotonergic neurons project to the spinal cord (traveling in the lateral funiculus) and provide tonic inhibition of sexual reflexes in the rat.

Orgasm

Seminal emission begins during arousal and, with continued sensory stimulation, orgasm is triggered, with ejaculation of the urethral contents resulting from the rhythmic phasic contractions of perineal and pelvic floor muscles. Ejaculation is effected by integrated sympathetic outflow from T11 to L2 segments traveling through the sympathetic chain and hypogastric plexus and along the pelvic and pudendal nerves, and by somatic efferents traveling through the pudendal nerves. Although the predominant neural control of the male accessory sexual organs is sympathetic (adrenergic and purinergic), the secretion of seminal fluid is under parasympathetic control. Sympathetic activity causes smooth muscle contraction in the seminal vesicles, vas deferens, and prostate to deliver seminal fluid to the posterior urethra; in the bladder neck to prevent retrograde ejaculation; and in the corpora cavernosa to cause detumescence. The latter "antierectile" activity is inhibited during erection through spinal coordination of reflex action.

The female orgasmic response consists of rhythmic contractions of pelvic floor muscles, the uterus, fallopian tubes, and paraurethral glands; expulsions from the paraurethral (Skene) glands through the urethra may occur (so-called female ejaculation). Women may achieve orgasms by stimulation outside the genital region and probably do so more easily than men, but the most notable difference from men is that women may achieve multiple consecutive orgasms.

Motor innervation of the pelvic floor muscles as well as the ischiocavernosus and bulbocavernosus muscles is conveyed through pudendal nerve branches from below. However, the most relevant motor innervation of the levator ani ("pelvic floor") muscle is directly from the sacral plexus via the levator ani nerve. Electromyographic recording of the pelvic floor muscles in women during vibratory clitoral stimulation shows intermittent activity associated with contractions on a background of continuous activity. During ejaculation in males, repeated bursts of electromyographic activity precede and follow expulsion of semen. The sensation of orgasm, however, is not dependent on pelvic muscle contractions. Men report that orgasmic sensation begins before, and lasts longer than, bursts of electromyographic activity in the perineal muscles.

Orgasm can be separated conceptually (but not easily physiologically) from emission and ejaculation. PET imaging during orgasm has shown deactivation of frontal regions and the left temporal lobe; cerebellum and pons were activated (Fig. 30-2). There were only minor differences between the sexes.[2]

After orgasm (during the "resolution" or "refractory" phase), fMRI reveals activation of amygdala and the temporal lobes, and—for a short period—of the septal area.

Anorgasmia is very rare in neurologically normal men, but 13 percent of women between the ages of 18 and 26 years have never achieved orgasm, with the incidence declining to a minimum of 3 percent in women between the ages of 51 and 64 years.[3]

Ejaculation can be absent with an intact orgasm in lesions of the hypogastric plexus and under the influence of some drugs.

Topographic Anatomy of Nerves in the Pelvis

Preservation of the peripheral nerves related to sexual (and bladder and bowel) function during

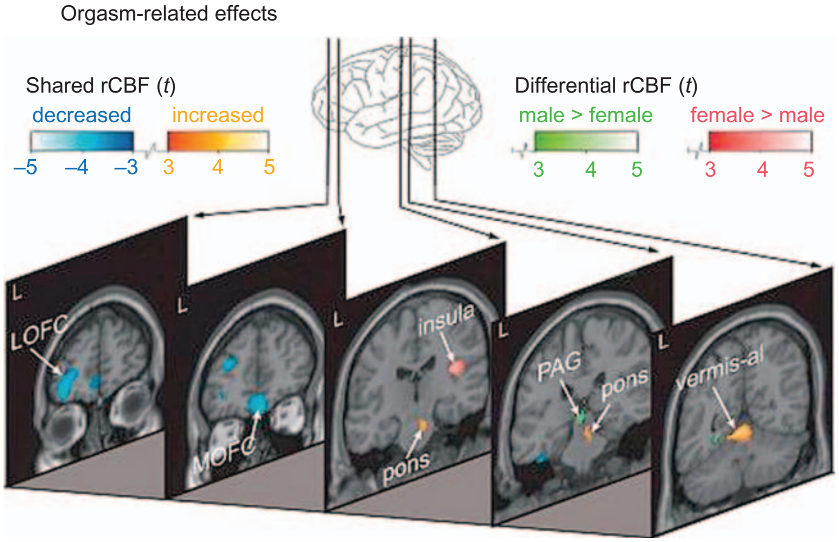

FIGURE 30-2 ■ Functional neuroimaging during male and female orgasm. Orgasm-related effects were evaluated by comparing scans of orgasm with scans of sexual tactile genital stimulation. Activated *(orange)* and inactivated *(blue)* areas are the same in men and women. However, certain parts of the brain are more active only in men *(green)* or in women *(red)*. LOFC, Lateral orbitofrontal cortex; MOFC, medial orbitofrontal cortex; PAG, periaqueductal gray; rCBF, regional cerebral blood flow. (From Georgiadis JR, Reinders AA, Paans AM, et al: Men versus women on sexual brain function: prominent differences during tactile genital stimulation, but not during orgasm. Hum Brain Mapp 30:3089, 2009, with permission.)

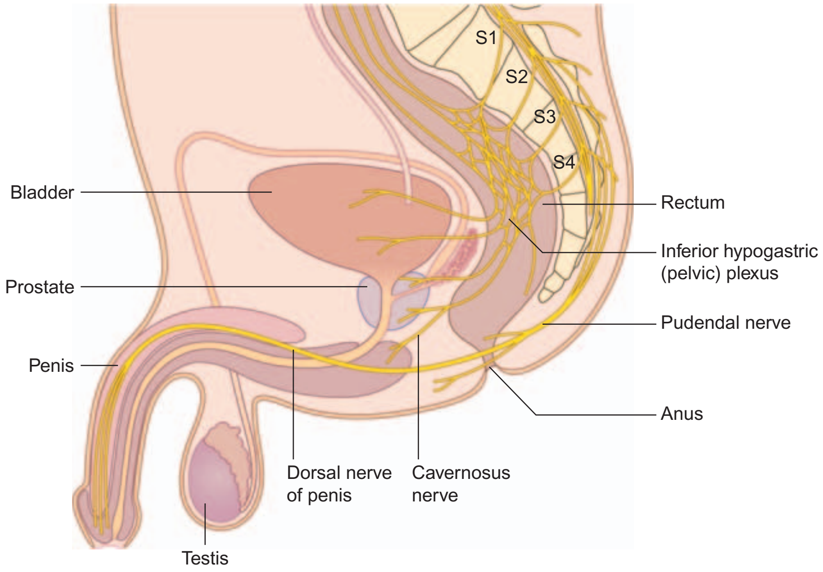

FIGURE 30-3 ■ Anatomy in males of the pudendal nerve (indicating its vulnerability to compression during cycling), and of the pelvic plexus and cavernous nerves (indicating their vulnerability during perineal or pelvic surgery).

abdominal and pelvic surgery is necessary for good postoperative results. In the pelvis and abdomen, autonomic structures related to genital innervation are situated in the retroperitoneal space. The superior hypogastric plexus is located anterior to the aortic bifurcation at the level of the fifth lumbar vertebral body and sacral promontory between the common iliac arteries. It divides caudally into the right and left hypogastric nerves. Within the pelvis, these nerves become the inferior hypogastric (pelvic) plexus, which is joined on each side by the pelvic nerves. In males, the inferior hypogastric plexus is lateral to the rectum, seminal vesicle, prostate, and the posterior part of the urinary bladder (Fig. 30-3). The lesser and greater cavernosal nerves originate from the anterior part, are joined by fibers from the pudendal nerves, and pass below the pubic arch. In females, the inferior hypogastric (pelvic) plexus gives off uterine nerves, branches for the vagina and cervix, and connections with the paracervical plexus.

In order to preserve neural structures relevant to sexual function during surgical procedures, the anatomy must be understood, surgical technique must be meticulous, and specific intraoperative "mapping" and "monitoring" procedures may be required.

Further details on the anatomy and physiology of the sexual response in men and women are provided elsewhere.[4,5]

Change in Sexual Function With Aging

There is little research on sexual functioning in the elderly. It is not easy to disentangle the changes due to aging and its related psychosocial problems from those due to any of the many different disorders that are common in the elderly (such as hypertension, cardiovascular disorders, lower urinary tract dysfunction, and depression) or to the effects of medication. Regardless, the sexual habits, desires, and preferences of the reasonably healthy elderly do not change, but the frequency of sexual activity generally decreases. Only 26 percent of those aged 75 to 85 years report sexual activity during the previous 12 months.[6] Men need more time and greater stimulation to achieve and maintain erections and to reach orgasm. They have a decreased sensation of impending ejaculation and decreased ejaculatory volume. Their refractory period after detumescence is prolonged. Their testosterone level decreases (but exogenous administration of androgens does not increase libido). Hormonal changes in menopausal women lead to loss of pubic hair and a change in the distribution of body fat tissue; libido diminishes and the vaginal wall thins, with decreased elasticity and lubrication. In some women, however, libido may actually increase after the menopause. In fact, 74% of women above 65 years of age continue to engage in sexual activity at least once a week.[6] Decreased sexual thoughts and frequency of intercourse after menopause are more closely correlated with testosterone than estrogen levels, but there is no clear relationship between low sexual desire and serum testosterone. In the very old (80 to 102 years old), touching and caressing is the most common form of sexual expression.

EVALUATION OF PATIENTS WITH SEXUAL DYSFUNCTION AND NEUROLOGIC DISORDERS

The breadth of the history and clinical examination will be tailored by the individual physician's interests and practice habits, but inquiry about sexual function should not be reserved for male patients. With the advent of effective treatment for erectile dysfunction, many physicians take a pragmatic approach to treatment and inquire about little more than whether erectile dysfunction is present. However, there is more to sexual dysfunction than erectile dysfunction, and more to treating any dysfunction than simply prescribing a pill. Dysfunction in an individual patient—even in the presence of neurologic disease—may be due entirely or in part to psychosocial, vascular, endocrine, or other causes.

History

The history should include details of neurologic disease as well as any past history of urologic/gynecologic, cardiovascular, endocrine, psychologic, and psychiatric disturbances. History of disorders of the sex organs, trauma and surgical procedures, the use of prescription drugs, smoking and alcohol habits, and possible drug abuse should also be elicited. The patient's sexual expectations, needs, and behavior should be defined as well as any misconceptions. Before diagnosing dysfunction of sexual organs, the level of actual desire should be established. The term *hypoactive sexual desire disorder* (HSDD) is used to define a persistent or recurrent reduction in desire for sexual activity, alone or with a partner, with inability to respond to sexual cues that would be expected to trigger a sexual response; these symptoms need to cause personal distress. If present in men, the disorder may be associated with impotence; in women it often occurs with the female sexual arousal disorder (FSAD), which is a persistent or recurrent inability to attain or maintain sufficient sexual excitement that causes personal distress.

Men should be asked about erectile function (the occurrence of nocturnal erections, morning erections, and erections evoked by genital, visual, auditory, or psychogenic stimuli) and women about vaginal lubrication. The nature of ejaculation should be determined, and in particular whether it is premature, retarded, absent, or dribbling (i.e., emissions occur through the urethra without the activity of pelvic floor muscles). Retrograde ejaculation, described as "dry ejaculation," means that ejaculum has entered the bladder. Finally it should be clarified whether the patient can achieve orgasm, and the quality of orgasmic sensations and experiences should be noted. In some circumstances it may be helpful to interview the patient's partner.

Formal questionnaires can be used to obtain standardized information on male and female sexual function. They are particularly relevant in research.

Clinical Examination

Sexual development, height and weight, changes in pigmentation and body hair, and the presence of galactorrhea should be noted. The external genitalia should be examined. Palpation of peripheral pulses (arms, legs, penis), auscultation of the heart, and blood pressure measurement are recommended.

A standard neurologic examination, with inspection of the lower back (for nevus, hypertrichosis, or sinus), the feet (for deformity or muscle atrophy), and the anogenital area may reveal signs of underlying neurologic disease. Examination of the anogenital region involves palpation of the bulbocavernosus muscles in the male, testing for voluntary contraction ("move the penis") and reflex contraction. The anal sphincter (also levator ani) is palpated for tone, voluntary contraction, and reflex contraction in both sexes by rectal examination. The cremasteric reflex (the L1 segment) and the bulbocavernosus and anal reflexes (S2 to S4/5 segments) should be tested.

Investigation of Genital Reaction and Arousal

In men, spontaneous and physiologically induced erection can be studied with a variety of techniques. Spontaneous nocturnal penile tumescence and rigidity can be measured in the sleep laboratory using mercury strain gauges (measuring penile expansion), visual inspection, measurement of buckling force (for assessment of rigidity), and polygraphic confirmation of sleep phases. Continuous monitoring of nocturnal penile tumescence and rigidity can be obtained by a rigidometer during normal sleeping conditions at home and also during daytime napping or in the awake, sexually stimulated state. Various low-cost screening tests for nocturnal penile expansion have been proposed, but their validity is questionable. Testing for nocturnal erections, however, does not reliably distinguish psychologic from central nervous system (CNS) causes of erectile dysfunction. The aforementioned testing remains mainly of research interest.

An intracorporeal penile injection of a vasoactive substance, such as prostaglandin E_1, will induce an erection (in the absence of major vascular pathology), thus strengthening the suspicion of a neurogenic or psychogenic cause of erectile dysfunction. Intracorporeal injection of vasoactive agents has been proposed as an established diagnostic tool in patients undergoing assessment for possible neurogenic erectile dysfunction and is safe when performed by experienced physicians, with an acceptable complication rate.

Suspected vasogenic erectile dysfunction may require the testing of penile vasculature (blood pressure and vascular competence) by a urologist. The purpose of testing should always be defined; pharmacologic testing may be sufficient for the majority of patients, and invasive tests reserved for those in whom surgery is contemplated.

In women, both direct and indirect methods are used to measure blood-flow changes in the labia and vagina. Noncontrast dynamic magnetic resonance imaging (MRI) can assess female sexual arousal quantitatively. All these tests are only of research interest; it has been stressed that vaginal vasocongestion to erotic stimuli may be unaccompanied by erotic feelings, and subjective indices should therefore be obtained when physiologic measurements are made.

Investigations of Neurologic Function

Functional tests are direct extensions of the clinical examination. Special devices and algorithms can be used for quantifying sensory perception on the genital organs and in the perineum. The measurement of vibratory perception (biothesiometry; measuring the vibration perception threshold) on the glans has been advocated for diagnosing sensory neuropathy in male and female patients. The vibration perception threshold on the penis (glans and shaft) in neurologically healthy men is similar to that of the feet, whereas in females this threshold (best measured on the clitoris, labia majora, and perineum) is the same as in the hands. Tests evaluating small-fiber function (e.g., testing for penile thermal sensation) may be more informative about the neural control of erection.

TABLE 30-1 ■ Tests for Assessing Sacral or Suprasegmental Neural Lesions

Somatic Sensory
Quantitative sensory testing
Dorsal penile nerve neurography
Pudendal somatosensory evoked potentials
Visceral Sensory
Somatosensory evoked potentials to proximal urethra/bladder neck stimulation
Bladder sensitivity testing
Somatic Motor
Electromyography
Motor evoked potentials
Sacral Reflex
Bulbocavernosus reflex
Anal reflex
Sacral reflex to proximal urethra/bladder neck stimulation
Autonomic
Sympathetic skin response
Neurocardiac testing
Cystometry

Several neurophysiologic tests have been suggested for assessing sacral or suprasegmental lesions (Table 30-1). Tests measuring conduction through somatic nervous pathways (motor, sensory, and reflex) might be expected to be useful because most lesions should involve both somatic and autonomic neural pathways, and abnormalities obtained on testing the former could be extrapolated to the latter. Even so, these tests are sensitive only to demyelination and not to axonal lesions, which predominate in clinical practice. Electromyography may demonstrate the activation patterns of striated muscles but is mainly used to differentiate normal from denervated (reinnervated) muscle. Controversy exists about the source and nature of the signals recorded in penile and clitoral electromyography, and the findings have no diagnostic relevance. The lumbosacral sympathetic system may be tested by the sympathetic skin response from the perineum (and penis).

The role in clinical practice of these and the other tests shown in Table 30-1 is limited. In terms of validity, experience, and available normative values, only electromyography (in muscles of the lower sacral myotomes) and the recording of sacral reflex responses and somatosensory evoked potentials (SEPs) to pudendal nerve stimulation are recommended. The patients with possible or probable neurogenic sexual dysfunction in whom such testing might yield a result relevant for diagnosis and prognosis (though rarely important for decisions on therapy) are those with suspected lesions in the peripheral sacral reflex arc. In these patients, support for the presence or absence of a neurologic lesion can be obtained; this may have medicolegal implications. The relationship between a neurologic lesion (or, for that matter, any neurophysiologic test abnormality) and sexual dysfunction is complex; in women with multiple sclerosis, for instance, latency of pudendal (and tibial) SEPs fails to predict the extent of sexual dysfunction.

Hormone Measurement

When patients with sexual dysfunction have symptoms or signs indicating endocrine dysfunction, hormone assays—or rather, endocrinologic consultation—may be necessary. The hormones to be studied depend on the circumstances (sex, age, and onset and nature of symptoms).

SEXUAL DYSFUNCTION IN PATIENTS WITH NEUROLOGIC DISEASE

Sexual dysfunction, such as lack of libido (in both sexes), erectile dysfunction and disturbances of ejaculation (in men), and deficient lubrication, dyspareunia, and problems with orgasm (in women), is not uncommon in the general population. In patient populations with disorders of the CNS, the prevalence of sexual dysfunction is reportedly higher, although few comparative studies have been done.

Insofar as many neurologic diseases affect primarily elderly patients and also carry the burdens of any chronic affection, the sexual dysfunction "specific" to the neurologic lesion(s) has to be ascertained against the background of valid control groups.

Head and Brain Injuries

Some cognitive impairment, personality change, and sensorimotor disability may remain after traumatic brain injury. Sexual dysfunction (either as a consequence of the cerebral lesion or psychosocial factors) occurs at a significantly greater frequency in these individuals.[7] Decreased or increased sexual desire, erectile failure, and retarded ejaculation may occur, at least in part as a consequence of post-traumatic pituitary dysfunction. Frontal and temporal lesions seem to result more often in sexual disturbances than parieto-occipital lesions. Hypersexuality, disinhibited and inappropriate sexual behavior, sexually aggressive behavior, and changes in sexual preference sometimes follow basal frontal and limbic brain injury and may lead to sex offences. Bilateral anterior temporal lesions may result in the Klüver–Bucy syndrome with hypersexuality and pansexuality (i.e., sexual drive that is directed not only toward humans but also toward animals and inanimate objects).

Cerebrovascular Disease

Decline in desire and the frequency of intercourse after stroke is not unexpected; the best predictor of decreased sexuality between partners is the degree of dependence in activities of daily living. From various studies, about 75 percent of patients who were sexually active before the stroke report a subsequent decrease in coital frequency. Poor-sexual functioning may persist even with otherwise good improvement.

Many men become impotent after a stroke; orgasmic and ejaculatory dysfunction is also common. Both erections and ejaculation may return within a year after stroke. Decreased vaginal lubrication and inability to achieve orgasm occur in women.

Sexual problems after a stroke may be complicated by other deficits, poor-personal image, lack of coping and, particularly, depression.

Patients and their partners may avoid sexual intercourse out of concern that another stroke may be precipitated. The heart rate during sexual activity may exceed 180 beats per minute in men and reach similar values in women; the workload during sexual activity is similar to that of climbing stairs or walking briskly. Although the exact risk of stroke during sexual activity is not known, it seems to be low. Patients and their partners may thus be reassured that, in resuming sexual activity, the gains in most instances outweigh any slight risks. These issues should be addressed in counseling.

Hypersexuality after stroke has been described, but seems to be rare.

Epilepsy

Epilepsy is associated with sexual problems, more often in men than women. Various types of abnormal behavior, hypersexuality, and, most commonly, hyposexuality have been reported, particularly in temporal lobe epilepsy. Satisfaction with life and sexuality is better in patients who are seizure free. The extent to which social and psychologic factors bear on sexual dysfunction is not clear. It is helpful to determine whether disturbances relate to seizures or occur during the interictal period.[8]

SEIZURES AND SEXUAL SYMPTOMS

Arousal and intercourse can provoke an epileptic attack through several pathophysiologic mechanisms; sexual phenomena may occur as part of an epileptic seizure; and sexual behavior may change in epileptic patients. Hyperventilation accompanying sexual activity can provoke generalized epileptic seizures. Sexual fantasies as well as genital stimuli (masturbation) or orgasm may trigger reflex epilepsy. Sensations in the genital organs may be manifestations of a partial epileptic seizure arising from a genital sensory cortical area. Motor symptoms such as erection and ejaculation or the sensory experience of an orgasm may also occur, the latter particularly from right mesiotemporal foci.

Such events may be experienced by patients as sexual or nonsexual. Pelvic sexual movements, as a part of epileptic automatisms, or compulsive masturbation in front of others may occur during or after a seizure. Complex sexual experiences may occur during an epileptic seizure in patients with complex partial epilepsy, most often in patients with temporal lobe lesions. Sexual automatisms may also occur with frontal lobe lesions.

Deviant sexual behaviors (e.g., exhibitionism, fetishism, or violent sexual behavior) have been related to epilepsy and interpreted as ictal phenomena. Only a few cases have been reported, but the episodic nature of the behavior and its occasional disappearance after treatment favor a causal connection between the behavior and the epilepsy. Complex partial seizures usually occurred, and lesions were present in one or both temporal lobes. Deviant behavior sometimes correlates with the presence of continuous seizure discharges in the electroencephalogram (psychomotor status).

INTERICTAL PHENOMENA

Patients with epilepsy, regardless of gender, often report a loss of sexual desire, reduced sexual activity, or inhibited sexual arousal; the prevalence of these complaints varies in different studies. Sexual interest is more reduced in patients with left temporal lobe lesions. Paranoid delusions of a sexual nature (such as of being violated) occur in some epileptic patients.

In men with temporal lobe damage and epilepsy, however, desire is sometimes preserved but erectile function is impaired and ejaculatory dysfunction may occur. Nocturnal tumescence may be lost.

Antiepileptic drugs, especially the older agents (phenytoin, phenobarbital, primidone, carbamazepine, and valproate), may lead to hormonal changes (particularly increased estradiol and decreased free testosterone levels in men), as well as decreased sexual desire and performance in both sexes. Menstrual irregularities are common among women with epilepsy. Antiepileptic drugs may influence morphology and motility of spermatozoa. The effect of the newer anticonvulsant drugs on sexual function is claimed to be less (for instance, for oxcarbazepine and lamotrigine). Sexual function is occasionally restored by surgery for epilepsy.

Parkinson Disease

Bladder and bowel dysfunction in Parkinson disease is related to specific autonomic nervous system involvement, and the same is probably true for some of the abnormalities in sexuality. The dopaminergic system is intimately involved in neural circuits controlling desire and arousal. Parkinsonian patients of both sexes show a decrease in libido, frequency of intercourse, and ability to reach orgasm. In men, erection and ejaculation are disproportionately affected. Women with parkinsonism report difficulties with arousal, vaginal tightness, involuntary urination, and sexual dissatisfaction. Depression is common in parkinsonian patients and may affect sexual activity; its treatment may further compromise sexual function.

Tremor may be enhanced during sexual arousal, thereby limiting the patient. Muscle rigidity and bradykinesia may also make sexual activities more difficult and may be worse in the late evenings if dose scheduling is aimed at favoring daytime activities.

Dopaminergic treatment may result in an apparent increase, or normalization, of libido without a corresponding improvement in parkinsonism. A true increase in desire and hypersexuality may occur as an adverse reaction to treatment with levodopa and, particularly, with dopamine agonists. On the order of 3 percent of treated patients demonstrate hypersexuality and probably even more do so among those treated with dopamine agonists; this has been attributed to D3 receptor hyperactivation. Spontaneous erections have been reported in patients receiving levodopa. Apomorphine treatment may result in erections and benefits sexual function, as does cabergoline.

Deep-brain stimulation of the subthalamic nucleus may have a positive influence on sexual well-being in Parkinson disease, in that male (but not female) patients are reportedly more satisfied with their sexual life. Hypersexuality has been reported as a side effect.

Multiple System Atrophy

Erectile dysfunction is an early sign of multiple system atrophy and indeed is the most frequent first symptom, beginning several years before the diagnosis is made (meaning that it often develops in men in their early 50s or late 40s). By the time of diagnosis, a large proportion of male patients were also unable to ejaculate. In women, reduced genital sensitivity (as compared to parkinsonian patients and controls) has been reported.

Patients have a decrease in desire, the ability to reach orgasm, and the frequency of intercourse. They may, however, develop hypersexuality with dopaminergic treatment.

Other Extrapyramidal Disorders

In families with Huntington disease, members who ultimately develop the disease tend to have more children than those who are spared. Approximately 10 percent of patients with Huntington disease have increased sexual activity, sometimes associated with mania or hypomania. Habitual promiscuity and marital infidelity may be early or initial symptoms of the disease. However, patients may have difficulty in becoming sexually aroused. Paraphilias such as sexual aggression, exhibitionism, and pedophilia may occur.

Disinhibited sexual behavior is common in patients with Gilles de la Tourette syndrome, and increased sexual activity has been reported in patients with Wilson disease.

Hypothalamic and Pituitary Disorders

Hypothalamic or pituitary dysfunction is usually caused by a pituitary adenoma; less common types of tumors in this region include craniopharyngiomas, meningiomas, optic gliomas, hypothalamic hamartomas, and metastases. Three-fourths of patients with hypothalamic or pituitary tumors have decreased or absent libido at the time of diagnosis. The figures are higher for large tumors that extend into the suprasellar region than for intrasellar tumors. Decreased libido (related to low serum testosterone levels) is also the first symptom in most men with small pituitary tumors and hyperprolactinemia, but is not a symptom for which patients commonly seek medical advice. Hence, the diagnosis is usually postponed until other symptoms appear, and it may be as long as a decade after the onset of changes in sexual behavior before the pituitary tumor becomes apparent. Erectile dysfunction is also common but, because of reduced sexual interest, is less distressing.

Most women with hypothalamic or pituitary disorders have amenorrhea. Women with hypoprolactinemia reportedly complain more commonly of loss of sexual desire than those with normal serum prolactin levels.

A low serum testosterone level in patients with erectile dysfunction does not necessarily signify a space-occupying lesion in the hypothalamic or pituitary region: a neuroimaging study of 164 impotent men with repeatedly low serum testosterone levels detected potentially serious lesions (pituitary lesions greater than 5 mm or any hypothalamic lesion) in 11, including 5 pituitary microadenomas (5 mm or more), 4 pituitary macroadenomas, and 2 hypothalamic lesions.[9]

Multiple Sclerosis

Disturbances of sexual function are common in patients with multiple sclerosis, regardless of gender, and affect eventually the majority of patients.[10] Sexual dysfunction decreases the patients' quality of life. Most such disturbances are thought to relate to spinal cord involvement and are generally, but not always, associated with urinary symptoms and lower limb involvement. Sexual dysfunction has also been correlated with destructive lesions in the pons, as detected by MRI, in patients with relapsing-remitting multiple sclerosis.

Erectile dysfunction is rare initially, but becomes more common with evolution of multiple sclerosis. Interest in resuming sexual activity persists in most patients. Spontaneous improvement in erectile function sometimes occurs. Problems with ejaculation are frequent and are often coupled to the erectile dysfunction. Anorgasmia has been correlated with evidence on MRI of brainstem and corticospinal abnormalities as well as with total area of lesions.

Decreased vaginal lubrication and sensory disturbances involving the genital region (hypoesthesia, hyperesthesia, and different types of pain) are common and may be apparent already in the early stages of multiple sclerosis. Sacral-segment dysesthesias may be so severe that patients are unable to bear direct genital or nongenital contact. Electrodiagnostic data—cortical evoked potentials of the dorsal nerve of the clitoris—suggest that pudendal somatosensory input is necessary for female orgasmic function, and that this may be disturbed even in early MS.

Some patients experience decreased libido; emotional and cognitive disturbances may be contributory. Increased sexual desire occasionally constitutes a problem. Other symptoms related to multiple sclerosis, such as fatigue, depression, cognitive dysfunction, spasticity in the lower limbs, urinary and bowel disturbances, and the use of aids to manage incontinence, can inhibit sexuality, as can paroxysmal motor and sensory disturbances triggered by sexual intercourse.

Lesions of the Spinal Cord

A spinal cord injury or lesion may lead to major neurologic deficits that in men initially often overshadow sexual disturbances such as a loss of normal erectile and ejaculatory function and of the ability to procreate naturally. For women, the resulting sexual dysfunction is often regarded as less limiting but is definitely important. The effects on erection, ejaculation, vaginal lubrication, and orgasm relate to the level and completeness of the lesion.

After complete cord transection, reflex function in all segments of the isolated spinal cord is completely lost (spinal shock) for a variable period lasting from a few hours to several weeks. Incomplete or slowly developing lesions may be associated with little or no spinal shock. The male genital reflexes (reflex penile erection and the bulbocavernosus and cremaster reflexes) are abolished or profoundly depressed during the period of spinal shock, and erectile and ejaculatory functions are abolished. Because of the occurrence of spinal shock, it is usually impossible to predict the extent or severity of sexual dysfunction, including whether erectile and ejaculatory functions will recover, in men within the first weeks after injury. With complete lesions of the spinal cord, the penis may become enlarged and semierect from passive engorgement of the corpora cavernosa due to paralytic vasodilation after the interruption of vasoconstrictor fibers in the anterolateral tracts of the spinal cord. As spinal shock subsides, reflex activity and spasticity may develop in the lower extremities and reflex functioning is regained of the bladder and bowels. In patients with upper motor neuron lesions, the erection reflex becomes part of the autonomic function of the isolated cord and may appear with tactile stimuli of various types and intensity, including stimuli to the penis, independent of cerebral participation and before the reflex responses of skeletal muscles are fully developed.

With complete destruction of the lower sacral spinal cord segments (the conus medullaris), reflex erection and lubrication are usually lost and the striated ejaculatory muscles are paralyzed. With spinal cord lesion between the level of the lower thoracic segments and the conus, both cerebral and reflex erection and lubrication may be possible, even though the patient cannot feel the sexual organs. Loss of sacral sensation does not necessarily imply anorgasmia. Although ejaculatory contractions cannot be felt when a complete lesion of the spinal cord exists above the conus, autonomic components of the orgasm can be experienced. Hyperesthesia often occurs just above or at the level of the spinal cord lesion, and may be useful as an erogenous zone. Although bladder, bowel, and sexual dysfunction often co-exist, this is not necessarily the case; sexual function may be preserved in spite of severe neurogenic bladder dysfunction, presumably owing to preservation of the thoracic sympathetic outflow.

A meta-analysis of 24 studies of more than 2,500 men with spinal cord injuries showed that a median of 80 percent (range, 54 to 95%) reported spontaneous erections.[10] The percentage of men reporting ejaculation without therapeutic assistance was much lower (median, 15%; range, 0 to 52%). Fewer (26%) of the patients with complete lower sacral lesions had erectile capacity than those with complete upper cord lesions or incomplete lesions at any level (90 to 99%). However, there is much individual variation, and an accurate prognosis for future sexual function may not be possible in individual cases.

Patients with incomplete spinal cord injury retain the ability for psychogenic genital vasocongestion if pinprick sensation is preserved in the T11 to T12 segments; only reflexogenic responses are obtained in those with complete spinal cord injury. After spinal cord injury, women menstruate and are able to conceive and give birth, although those with a paralyzed pelvic floor are at risk of overstretching and perineal tears. Autonomic hyperreflexia (Chapter 8) may occur in those with a lesion above T6 or T7.

Preoccupation with future sexual performance occurs early after injury, and it may be easier for men to accept motor deficits than sexual problems. Sexual readjustment depends on the individual, on previous sexual habits, and on the cooperation of partners. In one study, sexual readjustment was closely and positively correlated with a young age at injury, frequency of sexual intercourse, and willingness to experiment with alternative sexual expressions. Physical and social independence and a high mood level were further positive determinants of sexual adaptation after injury.[11]

The semen of men with spinal cord injury is characterized by small volume, low sperm count, and low sperm mobility. Reduced fertility cannot therefore be attributed completely to ejaculatory dysfunction. Collection of semen very early after the injury makes it possible to store semen of good quality for future insemination.

The ability to ejaculate by masturbation or sexual intercourse is impaired in most men with severe injury of the spinal cord; consequently, pregnancies caused by such men are rare without medical intervention. Ejaculation can be provoked in many paraplegic men through vibratory stimulation or electrostimulation (with careful blood pressure monitoring because of the risk of autonomic dysreflexia). Repeated vibration-induced ejaculations result in increased volume of semen, a larger number of motile sperms, and improved sperm penetration capacity. Insemination with autologous semen obtained in such a way has resulted in pregnancies.

Orgasms may occur in men with spinal cord injury but may differ from those that occurred before the injury. Women with such injuries may also achieve orgasm; indeed, some women with apparently complete lesions can do so, perhaps because of afferents from the cervix traveling with the vagus nerve. Latency to orgasm is greater in women with spinal cord injury than in normal subjects, but the descriptions of orgasm are indistinguishable.

Cauda Equina Lesions and Lumbar Stenosis

Although complete lesions of the cauda equina damage the parasympathetic erectile pathways to the penis, a number of men (approximately one-fourth) are still able to achieve an erection psychogenically, mediated probably by the sympathetic erectile pathway involving the hypogastric plexus. There are also ejaculatory disturbances (delayed or absent, but occasionally premature ejaculation), penile sensory loss, paresthesias, dysesthesias, and even pain syndromes. In a group of men with cauda equina lesions of differing causes and variable severity, only 15 percent reported normal sexual function.[12] Women report loss of erotic sensation, dyspareunia, loss of lubrication, loss of feeling during vaginal intercourse, difficulties in achieving orgasm, and changes in the feeling of orgasm.

Involvement of lower sacral nerve roots by any process can lead to “positive” as well as “negative” functional symptoms. Sensory symptoms and deficits involving the genitals are not necessarily accompanied by impotence. Spontaneous erections on walking are occasionally reported in patients with symptomatic lumbar stenosis.

Spinal Malformations

Any type of dysraphism may be associated with neurologic symptoms that may include sexual disturbances, but data from large patient populations are lacking. Meningomyelocele as a rule gives rise, among other disturbances, to sexual dysfunction, depending on the severity of the malformation. Some boys have no genital sensations at all, with loss of erection and orgasm; some have isolated erections without emission. Loss of genital sensations is the major complaint in girls.

Erectile dysfunction may occur in patients with Arnold–Chiari malformations; the onset of sexual symptoms is generally after the development of other neurologic disturbances.

Localized Nerve Lesions

Trauma may cause pudendal nerve injury, leading to loss of penile sensation, dysesthesias, pain syndromes, and dribbling ejaculation because of perineal muscle denervation. Among long-distance cyclists, it was found in one study that 22 percent had penile sensory symptoms and 13 percent had erectile dysfunction; symptoms were transient but persisted for up to 8 months.[13]

Erectile dysfunction may follow pelvic fracture, especially when urethral injury has occurred, owing to involvement of the neurovascular bundles. The peripheral autonomic nerves to the genitalia may be injured also by surgical procedures, leading to erectile and ejaculatory dysfunction in men and loss of lubrication in women. The sympathetic thoracolumbar fibers may be injured by retroperitoneal lymph node dissections. Pelvic plexus and cavernosal nerves may be injured by such operations as abdominoperineal resection for carcinoma, hysterectomy, radical prostatectomy, or sphincterotomy, thus significantly impairing the quality of life in patients after otherwise successful surgery (cf. Fig. 30-3). Surgeons are increasingly aware of the need to preserve relevant neural tissue even during radical surgery and have developed "nerve-sparing" operations.

Erectile dysfunction has also been reported after injection of sclerosing agents to treat hemorrhoids and hypersensitive bladder.

Diabetic Polyneuropathy

Diabetes is the most common cause of polyneuropathy in developed countries, and the most frequent type of neuropathy is the distal symmetric sensorimotor variety, in which small nerve fibers may be involved earlier than large fibers. This polyneuropathy is frequently accompanied by autonomic involvement, and dysautonomia is occasionally the predominant clinical presentation, with bladder, bowel, and sexual dysfunction. Hyperglycemia and some glycosylation products promote inactivation of nitric oxide and there seems to be a selective nitrergic neurodegeneration in diabetes. Further discussion of diabetic neuropathy is provided in Chapter 19.

Sexual dysfunction, especially erectile dysfunction, is common in diabetic men. Erectile dysfunction has been reported in 9 percent of diabetic men aged 20 to 29 years, rising to 95 percent of diabetics by age 70. Overall the incidence in a population of 9,500 diabetic men (20 to 70 years old) was 38 percent. Patients had the onset of impotence within the first 10 years of their disease in 50 percent of cases.[14] Men with diabetic polyneuropathy have fewer sleep-related erections, shorter tumescence time, diminished penile circumference increase, and weaker penile rigidity than do nondiabetic men. Erectile dysfunction is usually considered neurogenic when there are other signs of neuropathy, although alternative etiologic possibilities cannot be excluded. There is little correlation with neurophysiologic abnormalities in peripheral nerve function. Although the bulbocavernosus reflex latencies and penile (pudendal) evoked potentials are more often abnormal in impotent than potent diabetic men, neurophysiologic testing of pudendal nerve function is less sensitive in diagnosing neuropathy in impotent diabetics than limb nerve conduction studies.

In patients with cystopathy, retrograde ejaculation is sometimes an additional problem; failure of normal closure of the bladder neck by sympathetic activation during ejaculation leads to semen passing retrogradely into the bladder.

Among women, those with more diabetic complications have greater sexual dysfunction. A correlation in diabetic women of sexual dysfunction with the presence of neuropathy has not been found in all studies. Reduced sexual desire, decreased vaginal lubrication, and decreased capacity to achieve orgasm compared with age-matched controls have been reported.

Chronic Renal Failure

Male patients on hemodialysis have a similar prevalence of erectile dysfunction (approximately 70%) to patients on peritoneal dialysis (80%). Neuropathy is not the only possible cause; primary hypogonadism has been reported, and involvement of the testes also leads to low sperm counts and azoospermia. However, even in nondiabetic men with erectile dysfunction who were undergoing hemodialysis, the etiology is usually neuropathic rather than endocrinologic or vascular. On the whole, there is a tendency for pre-existent erectile dysfunction to improve after transplantation.

Among women with uremia, one-half have decreased desire, and one-third have decreased lubrication; dysfunction improves after transplantation.

Other Acquired Polyneuropathies

Autonomic dysfunction, including erectile dysfunction, occurs in other peripheral neuropathies, including those due to infectious agents, chemical toxins, secondary amyloidosis, prescription or street drugs, and vitamin B_1 or vitamin B_{12} deficiency, or those that are parainfectious or paraneoplastic. Autonomic involvement may lead to erectile dysfunction in the Guillain–Barré syndrome and may also occur in patients with chronic inflammatory demyelinating polyneuropathy. Reversal of erectile dysfunction and penile sensory loss may follow effective treatment.

In persons infected with the human immunodeficiency virus (HIV), peripheral nerve disorders occur commonly and may be accompanied by a dysautonomia. Slowed sural and dorsal penile sensory conduction velocities suggest that neuropathy is important in the genesis of erectile dysfunction in HIV-positive men. Counseling and treatment may be especially important in AIDS patients with sexual dysfunction, since the use of condoms often precipitates the problem, and men are therefore unwilling to use protection.

Hereditary Polyneuropathies

Erectile dysfunction and ejaculatory problems may occur in patients with hereditary sensory neuropathy and Charcot–Marie–Tooth syndrome. Erectile dysfunction also occurs in primary amyloidotic polyneuropathy and adrenoleukodystrophies. Men with hereditary motor and sensory neuropathy and electrophysiologically proven involvement of the pudendal nerves may nevertheless have normal sexual function.

Amyotrophic Lateral Sclerosis

Sexual function is normal in men with amyotrophic lateral sclerosis. Even when severe weakness makes intercourse impractical, erection and ejaculation are possible through partner masturbation, and the sensation of orgasm may be experienced as normal. These factors are highly relevant with regard to the patient's quality of life and may be important in counseling patients and their partners.

Hereditary Neuromuscular Diseases

The early onset and progressive course of certain hereditary neuromuscular diseases may restrict psychosocial and psychosexual development and limit sexual activity. Nevertheless, the capacity for sexual satisfaction remains unaffected in many patients who survive to adulthood and consequently has led to more awareness of the need for appropriate counseling.

In Kennedy syndrome (X-linked bulbospinal muscular atrophy), gynecomastia is common and testicular atrophy, decreased libido, and erectile dysfunction may occur. Hypogonadism, diminished libido, erectile dysfunction, and amenorrhea occur in certain muscular dystrophies (myotonic dystrophy but also others) and in mitochondrial encephalomyopathies.

Adverse Sexual Reactions to Medications

Many medications used in patients with neurologic disorders have adverse effects on sexuality (Table 30-2).

TABLE 30-2 ■ The Effects on Sexual Function of Some Common Medications Used for Neurologic or Related Purposes

Drug	Effects on Sexual Function
Anticholinergics (e.g., for movement disorders, depression, overactive bladder)	Vaginal dryness
Antihypertensives	Erectile dysfunction
Antipsychotics	Erectile dysfunction Reduced libido
Antidepressants	
Selective/nonselective serotonin reuptake inhibitors	Reduced libido Anorgasmia Delayed ejaculation Erectile dysfunction
Duloxetine	Reduced libido Anorgasmia Delayed ejaculation Erectile dysfunction
Trazodone	Priapism
Tricyclic agents (e.g., for depression, pain)	Erectile dysfunction Reduced libido Anorgasmia Delayed ejaculation
Antiparkinsonian agents	
Levodopa, dopamine agonists	Hypersexuality
Amantadine	Reduced libido
Antispasticity agents	
Baclofen	Erectile dysfunction Delayed ejaculation
Dantrolene	Erectile dysfunction Reduced libido
Antiepileptic drugs	
Enzyme-inducing antiepileptic drugs (e.g., phenytoin, carbamazepine, barbiturates)	Erectile dysfunction Reduced libido
Valproate	Erectile dysfunction Reduced libido Anorgasmia
Topiramate	Erectile dysfunction Anorgasmia
Pregabalin	Erectile dysfunction Delayed ejaculation
Oxcarbazepine	Anorgasmia
Levetiracetam	Reduced libido
Lamotrigine	Hypersexuality*

*Improved sexual function has been reported when patients are switched to lamotrigine.

At least until recently, however, the occurrence of sexual dysfunction was rarely monitored in clinical drug trials, and our data are collated from postregistration use, mostly uncontrolled studies and case reports. Further discussion of this aspect is beyond the scope of this chapter.

THERAPY

Sexual dysfunction associated with neurologic disease often increases patients' distress. Discussion with patients and partners about their sexual life should be part of any rehabilitation strategy. In all instances, drug regimens should be reviewed for possible effects on sexual function. Sexual education, counseling, and specific suggestions about therapeutic methods are important, and should be provided by the treating physician. In a limited number of patients, referral to a sexual therapist may be indicated. Methods for sexual rehabilitation in the context of neurologic disorders have been described.[15]

Treatment of Neurogenic Erectile Dysfunction

The development of drug treatments by the oral and intracavernous routes has revolutionized the outlook for men with erectile failure.

In neurogenic erectile dysfunction, part of the problem may be penile sensory loss. Additional vibratory stimulation may help in producing a rigid erection sufficient for vaginal penetration. As a last resort, surgical treatment is also possible.

ORAL AGENTS

Specific phosphodiesterase-5 inhibitors continue to be developed to treat erectile dysfunction; the first was sildenafil. These drugs have already been used by several million men. The selective inhibitors of type 5 cyclic guanosine monophosphate phosphodiesterase augment the nitric oxide-mediated relaxation pathway in penile tissues by increasing available cyclic guanosine monophosphate in the corpus cavernosum. These medications therefore do not cause erection but enhance the response to sexual arousal. Sildenafil taken at bedtime also significantly increases nocturnal erections.

Sildenafil is an effective treatment for erectile dysfunction in men with diabetes, patients on dialysis and after renal transplantation, multiple sclerosis, Parkinson disease, spinal cord injury, spina bifida, and familial amyloidotic polyneuropathy. In men with erectile dysfunction after radical prostatectomy, sildenafil is ineffective when a nerve-sparing procedure was not performed on at least one side, but it is effective if the cavernous nerves were spared, although it may take up to 18 months to obtain the best response. Overall, its efficacy in patients with an organic etiology of erectile dysfunction was reported to be 68 percent, being lower in diabetics (59%) and in nonselected postprostatectomy patients (43%).[16]

Sildenafil (25, 50, or 100 mg) can be taken orally 1 hour before intended sexual activity. (Significant effects have been reported between 30 minutes and 4 to 6 hours after taking the medication.) It should be noted that a meal delays absorption of the drug, and so does slowed gastric emptying such as is seen in Parkinson disease and autonomic neuropathy. Treatment should be begun with 25 or 50 mg, and the same dose taken several times before it is increased. Dose-finding studies have demonstrated a dose-response curve. Sildenafil can be used repeatedly, and if used once or twice per week there should be no fear of tachyphylaxis.

In men with diabetes mellitus or spinal cord injury, vardenafil (5 to 20 mg) and tadalafil (2.5 to 20 mg) have been used with similar efficacy. Tadalafil has a longer half-life and is thus longer acting.

Phosphodiesterase-5 inhibitors are contraindicated in combination with vasodilator drugs of the nitro type and nitric oxide donors, but a cardiologist can change such drug regimens in suitable patients with erectile difficulties requiring treatment. Phosphodiesterase-5 inhibitors should not be used in patients with retinitis pigmentosa. They are contraindicated in men with hypotension (blood pressure below 90/50 mmHg). Care should be taken to identify men with multiple system atrophy who may have erectile dysfunction, atypical parkinsonism, and asymptomatic postural hypotension. In our experience, an intelligent patient can use sildenafil after clear explanation, with careful planning of activity during the several hours after drug intake and performing sexual activity in the recumbent position.

No evidence was found of sildenafil effects on the myocardium or the conduction system. However, evaluation of functional capacity is necessary in patients with coronary artery disease, who need to know the risks of physical (and sexual) activity. Patients who can exercise to 4.5 metabolic equivalents without angina or hypotension can probably use sildenafil safely. Recommendations for the use of sildenafil in patients with cardiovascular disease have been published. In controlled and open-label studies, no increased risk of cerebrovascular events has been reported, although one patient has shown a temporal association of sildenafil use with a transient ischemic attack and then a stroke.

The most common adverse events of sildenafil are headache, flushing, and dyspepsia. Temporary visual symptoms (mainly color-vision disturbances) may occur with higher doses (100 mg), and nonvasculitic anterior optic neuropathy has been described in rare instances. Adverse effects are mostly transitory and of minor intensity.

Treatment with apomorphine sublingually has been tried as another therapeutic option for men with erectile dysfunction, but it has a relatively weaker effect than phosphodiesterase-5 inhibitors, and obnoxious side effects (nausea).

Yohimbine is an ancient aphrodisiac that is produced from the yohimbine tree (*Pausinystalia yohimbine* of the Rubiaceae family), which grows in West Africa. It has little to offer in the presence of modern drugs.

INTRACAVERNOUS INJECTION THERAPY

Intrapenile injections of papaverine have been used extensively in the treatment of erectile dysfunction in men with spinal cord injury, multiple sclerosis, and other neurogenic conditions. Doses do not relate to the level or extent of spinal injury. Prostaglandin E_1, papaverine, and a papaverine-phentolamine mixture all showed an efficacy rate of more than 70 percent. Acute complications such as priapism were, however, lower with prostaglandin (25%) than papaverine (65%) or a papaverine-phentolamine mixture (63%); the risk of local long-term complications was also lower with prostaglandin (8%) than with papaverine (57%) or a papaverine-phentolamine mixture (12.4%).[17]

Prostaglandin E_1 (alprostadil) is now the preferred drug for self-injection therapy in erectile dysfunction. Intracavernous injection should be taught under medical supervision before self-administration is attempted by the patient or his partner. The effect is very rapid and may last for 2 to 4 hours. Its efficacy in diabetic patients with impotence has been confirmed. Local bleeding, pain, and fibrosis may develop in the corpora cavernosa, leading to loss of effectiveness. This treatment is contraindicated in patients taking anticoagulants or with hematologic malignancies.

Long-lasting erections—priapism—as an adverse drug reaction usually have a good prognosis with conservative treatment. Painless priapism of less than 6 hours' duration should be treated at first by cooling. If present for more than 6 but less than 24 hours, intracavernous injection of an α-adrenergic agonist such as metaraminol is recommended. In painful priapism or with failure of conservative methods, penile puncture should be performed, at which time a cavernosal blood sample should be obtained to assess cavernosal hypoxia.

INTRAURETHRAL THERAPY

Intraurethral therapy with alprostadil (prostaglandin E_1) has been introduced as a less invasive alternative; in a study of patients with spinal cord injury, it was found to be of variable effectiveness and less satisfactory than intracavernosal injection therapy.

VACUUM DEVICES

Rigidity adequate for penetration occurs in 90 percent of patients with neurogenic erectile dysfunction when a vacuum device is used. Satisfaction of partners was initially reported as high (70%), but after months of treatment, and despite an increase in sexual activity, only 41 percent of patients were satisfied.[18] Premature loss of rigidity and difficulty in placing and removing the constriction bands are common complaints. The most common complications are bruises, petechiae, and skin edema. The constriction band should not stay in place for longer than 30 minutes; major complications such as penile gangrene, severe erosion, and cellulitis have been associated with prolonged wearing of the band.

The use of a constriction band (on its own) may help patients who can obtain an erection, albeit not a durable one; the same restrictions concerning the duration of application should be observed.

SURGICAL TREATMENT

Penile prostheses (implanted semifirm or inflatable rods) were introduced in the 1970s, but, with the advent of pharmacologic treatment options, have limited utility in neurologic patients. They may still be useful as a last resort, but are not considered further here.

Ejaculatory Dysfunction in Men With Neurologic Disorders

In cases of anejaculation/anorgasmia, vibratory stimulation may be helpful. The presence of functional penile nerves is necessary for orgasm achieved by penile vibratory stimulation. (Interestingly, penile vibration has a significant antispastic effect.)

Diabetes mellitus, retroperineal lymph node resection, and certain pharmacologic agents may render the patient effectively sympathectomized, leading to failure of seminal emission or to retrograde ejaculation. Patients may respond to a variable extent to sympathomimetic pharmacologic agents such as imipramine, phenylpropanolamine, or ephedrine. If retrograde ejaculation persists, sperm retrieval from the bladder is usually all that is required when insemination is contemplated. If unsuccessful, procedures such as surgical sperm retrieval from the testis, epididymis, or vas deferens may be necessary. Such patients are usually poor candidates for the assisted ejaculation procedure of penile vibratory stimulation because the sympathetic innervation necessary for seminal emission is not intact.

Treatment options for insemination in other neuropathic conditions include assisted ejaculation or surgical sperm retrieval. The choice of treatment depends on the patient's ability to respond to methods of assisted ejaculation and on the quantity and quality of sperm in the ejaculate. With surgical methods, the assisted reproductive technology of intracytoplasmic sperm injection will probably be required owing to the low numbers of sperm obtained with these methods. Assisted ejaculation methods generally result in higher numbers of sperm, thus allowing for more assisted reproductive technology options.

Premature (or rapid) ejaculation has been associated with myelopathy and neuropathy, but is nowadays usually considered to be constitutional, with psychogenic contributory mechanisms. Counseling on the use of particular techniques may lead to improvement. Pharmacotherapeutic options include topical anesthetics, antidepressants (selective serotonin reuptake inhibitors such as paroxetine), and phosphodiesterase-5 inhibitors, all used off-label.

Treatment of Abnormalities of Libido

Hormone insufficiency, testosterone in men and estrogens in women, should be corrected. Hyperprolactinaemia should be treated.

For abnormally increased libido, pharmacologic treatment should be checked. Androgen antagonists (cyproterone acetate, medroxyprogesterone acetate) may be effective. In resistant cases, neuroleptics are usually helpful.

Treatment in Women With Sexual Dysfunction

Vibratory stimulation and dildos may be helpful and are routinely advised in patients with genital sensory disturbances and in those with weakness or motor disorders.

Sildenafil has been well-tolerated in women with neurologic disorders causing lack of sexual arousal, such as multiple sclerosis and spinal cord injury, with few benefits or side effects. In multiple sclerosis, there was an effect on lubrication, but quality of life did not improve significantly although some women opted to continue on the drug after conclusion of the study. Clearly sildenafil does not produce the same spectacular results in women as it does in men with disturbed sexual responses related to underlying neurologic disorders.[14]

In women with dysesthetic or painful sensations in the genitalia that are not alleviated by improving lubrication, antiepileptic drugs such as gabapentin, pregabalin, and carbamazepine may help. Women showing signs of estrogen insufficiency should be referred to a gynecologist for hormone replacement therapy.

NEUROLOGIC PROBLEMS ASSOCIATED WITH SEXUAL ACTIVITY

Headache

Headaches related to sexual activity must be treated as potentially serious because subarachnoid hemorrhage may occur during exertion and headaches of other cause may also be exacerbated in the sexual context. Vascular mechanisms are the probable cause of headaches that occur during sexual arousal in patients with unruptured aneurysms, cerebral tumors, and subdural hematomas. Pain due to angina pectoris or myocardial infarction may be referred to the head. Low-pressure postcoital headache, analogous to that following lumbar puncture, may also occur; symptoms are relieved by recumbency.

Regardless of cause, a headache developing for the first time during sexual activity, particularly if it is of sudden onset and occurs at orgasm, is usually alarming; many patients are convinced that they have had a cerebral hemorrhage. Luckily, most sexual headaches are benign and self-limiting.

The benign headache designated before as orgasmic or preorgasmic is a primary headache. It is commonly severe, usually sudden, pulsatile, bilateral, and located occipitally. Its mean duration is 30 minutes, but it may be quite short or last the entire day. A dull, long-lasting, tension-type discomfort can outlast the headache. The headache may be accompanied by nausea, vertigo, and other symptoms. Men are afflicted more often than women; the first peak of occurrence is early in the third decade, with the second late in the fourth decade. Comorbidity with migraine, tension-type headache, and exertional headache is common. The headaches may be recurrent, but spontaneous remission is the rule. Treatment with indometacin or propranolol is recommended.

Migraine may be triggered by sexual activity. Its character is identical to the patient's usual pattern of migraine. On occasion, sexual arousal forms part of the aura of migraine.

Ampoules of amyl nitrite, crushed and inhaled immediately before the event, are sometimes used in an attempt to enhance orgasm. A potent vasodilator, this drug may produce severe vascular headache. More often "sexual activity-associated" headache is nowadays a side effect of the use of phosphodiesterase inhibitors taken for treatment (or sport).

Transient Global Amnesia

Transient global amnesia is sometimes associated with a precipitating event. "Emotional" events predominate in women, "physical" events in men. Sexual intercourse may qualify for both categories and has been regularly reported among provoking events in both sexes.

CONCLUDING COMMENTS

Many questions regarding the neuroanatomy and neurophysiology of sexual function remain to be answered. The fine neural control of human sexual behavior by the cerebral hemispheres, brainstem, and spinal cord is still not elucidated. Tools to define the role of psychosocial and biologic factors (such as endocrine, neurologic, vascular, endothelial, and other factors) in the individual patient with sexual dysfunction are still crude. The options to help patients have nevertheless improved significantly in the last decades. Patients need the interest and support of their physicians in the realm of sexuality; they deserve no less.

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CHAPTER

31

Pregnancy and Disorders of the Nervous System

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EPILEPSY
- Effect of Pregnancy on Maternal Seizures
- Effects of Maternal Epilepsy on the Fetus
  - *Seizures*
  - *Fetal Malformations*
  - *Bleeding Disorders*
  - *Withdrawal Symptoms*
  - *Breast-Feeding*
- Management of Epilepsy
- Obstetric Management
- Interactions Between Oral Contraceptives and Anticonvulsants

MIGRAINE
- Acute Treatment
- Preventive Treatment
- Treatment During Lactation

TUMORS

IDIOPATHIC INTRACRANIAL HYPERTENSION

CEREBROVASCULAR DISEASE
- Occlusive Arterial Disease
- Occlusive Venous Disease
- Pituitary Infarction or Hemorrhage
- Disseminated Intravascular Coagulation
- Subarachnoid Hemorrhage from Intracranial Vascular Anomalies
- Intracranial Dural Arteriovenous Fistulas
- Spinal Arteriovenous Fistulas and Malformations

INFECTIONS
- Retroviral Infections
- Poliomyelitis
- Tetanus
- Other Infections

METABOLIC AND TOXIC DISORDERS

MOVEMENT DISORDERS
- Chorea
  - *Chorea Gravidarum*
  - *Other Causes of Chorea*
- Restless Legs Syndrome
- Dystonia
- Essential Tremor
- Parkinson Disease
- Tourette Syndrome
- Wilson Disease

MULTIPLE SCLEROSIS

OPTIC NEURITIS

TRAUMATIC PARAPLEGIA

ROOT AND PLEXUS LESIONS

PERIPHERAL NERVE DISORDERS
- Entrapment Neuropathies
- Traumatic Mononeuropathies
- Bell Palsy
- Polyneuropathies

MYASTHENIA GRAVIS

MYOTONIC DYSTROPHY

ECLAMPSIA AND PRE-ECLAMPSIA

Neurologic disorders may present first during pregnancy, and their investigation and treatment may be complicated by concerns for the safety of the developing fetus. Furthermore, the natural history of certain pre-existing diseases may be affected by pregnancy, and obstetric management may be influenced by the neurologic disturbance. These aspects are considered in this chapter.

Concerns about the use of imaging studies in pregnancy merit comment. In general, fetal exposure to ionizing radiation from computerized tomography (CT) is small, especially when the fetus is not in the imaged region. Magnetic resonance imaging (MRI) does not expose patients to ionizing radiation and may be necessary when the findings may influence clinical management during the pregnancy. Iodinated

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contrast may be administered during pregnancy when necessary for maternal care, but thyroid function tests should then be performed in the neonate in the first week of life. Gadolinium contrast passes into the placenta and may harm the fetus, so its use should be avoided when possible; otherwise, the smallest possible dose is given when required for maternal care.

EPILEPSY

Birth rates are lower and maternal mortality during pregnancy, delivery, or the postpartum period are higher among women with epilepsy that among nonepileptic women. Pregnancy may affect the natural history and management of patients with epilepsy in several ways. In addition, antiepileptic management may affect the developing fetus and obstetric management. Many pregnancies are unplanned, so that regular counseling of women with epilepsy during the reproductive years is important.

Effect of Pregnancy on Maternal Seizures

An increase in seizures occurs during pregnancy in 23 to 75 percent of cases depending on the series; seizure control is unchanged in between 53 and 67 percent. It is not possible to predict in advance whether or how seizure frequency will be altered during pregnancy, but certain general points can be made. Seizure frequency is more likely to increase in poorly controlled epileptic patients than in those with infrequent seizures, and in those with focal seizures; any increase is most likely to occur during the first trimester. Any change in seizure frequency usually reverses after the birth of the infant, although occasional patients whose seizures increase during pregnancy remain more difficult to control thereafter. For patients without seizures for at least 9 months prior to conception, the likelihood of remaining seizure-free during pregnancy ranges between 84 and 92 percent in different series.[1] The influence of a particular pregnancy cannot be predicted by the outcome of previous pregnancies, any relationship between seizures and the menstrual cycle, or maternal age. Seizures may occur for the first time during or immediately after pregnancy and in some instances occur only in relation to pregnancy. Even in patients with such true gestational epilepsy, however, it is not possible to predict the course of subsequent pregnancies from the occurrence of seizures during one pregnancy.

Status epilepticus may complicate pregnancy and sometimes occurs before there is any other evidence that seizures have become more difficult to control. It may take the form of tonic-clonic (major motor) or nonconvulsive status. The former is easy to recognize, but a transient alteration in mental status and level of arousal may not be attributed to nonconvulsive status epilepticus unless an electroencephalogram is performed. As in the nonparous woman, it is important to obtain control of the seizures rapidly, but therapeutic termination of pregnancy is usually unnecessary. There is no evidence that anticonvulsant drugs administered intravenously to treat status epilepticus affect the fetus adversely.

The reason that seizure frequency sometimes increases during pregnancy is not clear, but a change in drug requirements during the gestational period may sometimes be responsible. Pregnancy probably causes an increase in the clearance and a decrease in the blood concentrations of, for example, lamotrigine, levetiracetam, phenytoin, and, to a lesser extent, carbamazepine, and of the active oxcarbazepine metabolite, the monohydroxy derivative.[2] Zonisamide serum concentration may decline by more than 40 percent during pregnancy, especially in the last trimester, but there is much interindividual variability. Evidence of a change in clearance or blood level of phenobarbital, valproate, primidone, and ethosuximide is inadequate to permit a definite conclusion to be reached.[2] Other possible reasons for the increased dose requirements of anticonvulsants during pregnancy include poor compliance with the drug regimen, changes in drug absorption and excretion, and the dilutional effects of increasing plasma volume and extracellular fluid volume. Changes in drug absorption may relate to nausea, vomiting, or reduced gastric motility. Antacids are frequently prescribed during pregnancy and are known to adsorb to medications, preventing absorption. An increased metabolic capacity of maternal liver and metabolism of part of the anticonvulsant dose by the fetus, placenta, or both may also be important. Folic acid therapy (which may reduce the risk of major congenital malformations when taken preconceptionally[2]), prescribed routinely by many obstetricians, sometimes lowers the plasma phenytoin level.

Whether hormonal factors contribute to an increase in seizure frequency during pregnancy is unclear, but estrogens are epileptogenic in animals, and progesterone is said to have both convulsant and anticonvulsant properties. Finally, fatigue and sleep deprivation may influence seizure frequency during pregnancy.

The reason that seizure frequency decreases in some epileptic patients is also unclear, but improved compliance with the anticonvulsant drug regimen may be responsible.

Effects of Maternal Epilepsy on the Fetus

SEIZURES

A major concern in the management of epileptic women during pregnancy is the possible effect of the seizure disorder and of anticonvulsant drugs on the developing fetus. It is difficult to determine the precise risk that a seizure disorder will develop in the offspring of epileptic parents. The risk depends in part on whether the parental epilepsy is idiopathic (constitutional) or acquired; such risk appears to be increased among the offspring of epileptic mothers but not when only the father is epileptic. The reason for the increased risk is unclear, but genetic factors may be important, as may the consequences of maternal seizures or anticonvulsant drugs taken during pregnancy.

FETAL MALFORMATIONS

For many years, concern has existed that anticonvulsant drugs are teratogenic. Epidemiologic studies are difficult to interpret because epilepsy occurs for different reasons, varies in severity between patients and in the same patient at different times, may itself increase the risk of fetal malformation, and is treated by many drugs in different doses and combinations; environmental and genetic factors also bear on the development of fetal malformations and are difficult to control. Nevertheless, numerous reports suggest that certain anticonvulsant drugs are indeed teratogenic in humans, and the risk of malformation among the offspring of epileptic women is approximately double that for nonepileptic women. A greater teratogenic risk exists with polypharmacy, but specific antiepileptic drugs in the regimen may actually be more important than whether multiple drugs are taken.

The older antiepileptic drugs taken during the first trimester of pregnancy are probably all teratogenic to some extent, especially when taken in combination.[3] However, it cannot be determined whether the increased risk relates to all or to only some antiseizure medications. Trimethadione, which is now rarely used and should be avoided during pregnancy, is particularly dangerous and causes fetal malformations and mental retardation in more than 50 percent of exposed infants. The absolute risk of major congenital malformations is also especially marked for valproate,[3] which is associated with a high (1%) rate of neural tube defects and may also cause cleft lip or palate, polydactyly, hypospadias, craniosynostosis, atrial or ventricular septal defect, developmental delay, and other disorders; it is also associated with cognitive impairment and autism spectrum disorder. Its teratogenicity is dose dependent. Other antiepileptic drugs have different teratogenic risks. Phenytoin, phenobarbital, carbamazepine, and topiramate have been associated variously with cardiac anomalies and cleft palate, and carbamazepine with neural tube defects.[3–5] A longitudinal, prospective cohort study showed that the risks of major congenital malformation are lowest with lamotrigine and levetiracetam. Gabapentin, oxcarbazepine, and zonisamide are not associated with an increased risk, but the data concerning these medications are limited.[4] There are no or very limited data for newer drugs such as eslicarbazepine, lacosamide, perampanel, and brivaracetam. Vagal nerve stimulation therapy has not been associated with teratogenicity. These findings should guide the rational selection of medication in women with epilepsy, taking into account comparative risks and treatment alternatives.[6]

A specific syndrome has been described among some of the offspring born to mothers taking phenytoin, phenobarbital, or carbamazepine during pregnancy and bears some resemblance to the fetal alcohol syndrome. It is characterized by prenatal and postnatal growth deficiency, microcephaly, a dysmorphic appearance, hypoplasia of the distal phalanges, and mental deficiency. A characteristic facial phenotype in children exposed to valproic acid or sodium valproate in utero has also been described. Some of these children may have educational difficulties.

The mechanisms involved in teratogenesis of anticonvulsant drugs are not known but may include folate deficiency or antagonism and production of toxic intermediary metabolites during biotransformation of the parent compound. Specific oxidative intermediates such as epoxide, for example, have been suggested as the ultimate teratogen in patients receiving phenytoin.

BLEEDING DISORDERS

A clinical or subclinical bleeding disorder may occur in neonates exposed to anticonvulsant drugs in utero, without evidence of coagulopathy in the mothers. Although a number of anecdotal cases have been reported, the evidence is insufficient to determine whether the risk is, in fact, substantially increased in the newborns of women with epilepsy.[2] Bleeding has usually occurred within 24 hours of birth, sometimes in unusual sites (e.g., the pleural or abdominal cavities). Bleeding has also been reported to occur in utero, leading to stillbirth. However, it has been questioned whether maternal use of antiseizure medication leads to a coagulopathy at all, and certainly the evidence is insufficient to support or refute this association.[2] In any event, the routine intramuscular administration of vitamin K_1 (1 mg) to all newborns (regardless of maternal epilepsy) is sufficient to reduce the incidence in infancy of late vitamin K deficiency bleeding (previously designated hemorrhagic disease of the newborn), with its high morbidity and mortality.

WITHDRAWAL SYMPTOMS

Maternal use of certain anticonvulsants may be associated with withdrawal symptoms in the neonate, with restlessness, irritability, tremulousness, difficulty in sleeping, and vasomotor instability, usually beginning a few days after birth.

BREAST-FEEDING

Although certain anticonvulsant drugs (primidone, ethosuximide, gabapentin, lamotrigine, levetiracetam, topiramate, and zonisamide) taken by the mother may be present in breast milk, there is no evidence that these have symptomatic effects on the newborn or affect development.[2] Breast-feeding therefore need not be discouraged on this account; however, when obvious sedation develops in an infant that could relate to anticonvulsants in the maternal milk, breast-feeding should be discontinued and the child observed for signs of drug withdrawal. There is no evidence that phenobarbital, phenytoin, valproate, and carbamazepine penetrate the breast milk in a clinically important amount.[2]

Management of Epilepsy

Little or no information is available in the published literature to guide decision-making with regard to certain management issues in women with epilepsy. Epilepsy must be managed during pregnancy, as at other times, by prophylactic anticonvulsant drugs. Management should be by monotherapy whenever possible, with selection of the anticonvulsant that is most appropriate for seizure type. As indicated earlier, lamotrigine and levetiracetam seem to have the least teratogenic risk, and women of childbearing age should be managed on one of these drugs when feasible, depending on seizure type. There is little point in substituting one anticonvulsant drug for another after the first 2 to 3 months of pregnancy because major fetal malformations will probably have occurred already if they are going to occur at all. Folate supplementation may help, however, to reduce the risk of teratogenicity and of certain malformations (such as neural tube defects), although the optimal dose is unclear. Some prescribe 0.4 mg folate daily for all women of childbearing age from a month before conception to the end of the first trimester, whereas others prescribe 4 mg daily for 3 months before and after conception for those at particular risk because of family and past medical (including spousal) history, a previous baby with a neural tube defect, or because they are taking valproate or carbamazepine. Folate supplementation is followed by routine prenatal vitamin supplementation for the remainder of the pregnancy and during lactation.

Anticonvulsant drug treatment should be monitored during pregnancy by serial (monthly) measurement of plasma drug levels, depending on the drug that is being taken, as discussed earlier. Patients should be seen monthly, and as the pregnancy continues the dose of medication may need to be increased to maintain plasma concentrations at previously effective levels. If increases are made during pregnancy, dose reductions will be necessary at some point after delivery to prevent toxicity, but at a time that must be determined individually based on clinical evaluation and plasma drug levels. In general, lamotrigine and levetiracetam can be tapered over 2 to 3 weeks, and other antiseizure medications over about a month or longer, beginning 3 or 4 days after delivery.

If patients inquire, it is appropriate to indicate that there is a slightly increased risk of fetal malformation due either to the seizure disorder itself or to the drugs used in its treatment. Nevertheless, there is still a very good chance (90 to 95%) that offspring will be normal. It must also be emphasized that the risks to both mother and fetus of noncompliance with anticonvulsant drug regimen are considerable, in that an increased seizure frequency or even status epilepticus may occur, with its associated morbidity and mortality.

Obstetric Management

Most women with epilepsy will have a normal pregnancy and delivery. It is rare for seizures to occur during labor and delivery, but when they do occur it is usually in women who have continued to have seizures during the pregnancy.

Increased incidences of vaginal hemorrhage and toxemia and an increased stillbirth rate have been reported in epileptic women by some authors but not others. For those taking antiepileptic medication, the risk of cesarean delivery or late-pregnancy bleeding is increased but is less than double the expected risk, while the risk of premature contractions or premature labor and delivery is increased only mildly.[1] The increase in cesarean deliveries has been attributed to uncertainty in guiding the delivery of epileptic women and the misperception of an increased risk of complications. An increased incidence of neonatal death has sometimes been reported, perhaps owing to an increased incidence of congenital malformations, iatrogenic neonatal hemorrhage, the metabolic or toxic effects of seizures or anticonvulsant drugs, or socioeconomic factors.

Targeted ultrasonography can be used to diagnose most neural tube defects at 12 to 22 weeks of pregnancy as well as other major structural abnormalities.

Interactions Between Oral Contraceptives and Anticonvulsants

Certain anticonvulsants (including phenytoin, carbamazepine, felbamate, topiramate, oxcarbazepine, eslicarbazepine, perampanel, phenobarbital, and primidone) may alter the effectiveness of oral contraceptives, leading to unwanted pregnancy. Thus, the risk of contraceptive failure in patients taking these anticonvulsants should be discussed in advance and documented in the patient's records; in some instances, use of an additional backup contraceptive method should be considered, such as a condom, intrauterine device, or depot injection. The incidence of breakthrough bleeding is also increased in women taking these anticonvulsants and concurrent oral contraceptives, and such bleeding may point to the possibility of contraceptive failure. Oral contraceptives may also affect seizure frequency or blood levels of anticonvulsant medication (e.g., lamotrigine).

MIGRAINE

Migraine is more common in women than men and is often influenced by pregnancy. Most commonly, the frequency and severity of attacks improve after the first trimester, but occasionally migraine worsens or occurs for the first time during pregnancy. Occasionally, attacks are changed so that auras occur without headache. The influence of pregnancy on migraine does not depend on any relationship of migraine to the menstrual cycle. Similarly, it does not relate to the sex of the fetus or to differences in plasma progesterone levels, although there may be some relationship to changes in the pattern of circulating estrogens. The association between migraine and oral contraceptive preparations is discussed in Chapter 20.

Acute Treatment

Treatment of migraine during pregnancy is similar to that at other times, with emphasis on the avoidance of precipitating factors together with the use of simple analgesics as necessary. However, acetaminophen should be used in preference to aspirin because there is some evidence that aspirin use in large dosages in the later stages of pregnancy may prolong labor, increase the incidence of stillbirth, impair neonatal hemostasis, and cause premature closure of the ductus arteriosus. Nonsteroidal anti-inflammatory drugs (NSAIDs) also are best avoided. Some but not other studies in animals suggest that they may lead to congenital malformations and miscarriage when given in early pregnancy; after 30 weeks, they may cause premature closure of the ductus arteriosus and other adverse fetal outcomes.

Although early studies showed that sumatriptan in extraordinarily high doses led to death or malformations in fetal rats and rabbits, later retrospective studies and meta-analyses in humans provided no evidence either for teratogenicity or for prematurity or spontaneous abortions.[7] When acute treatment for migraine is required during pregnancy, sumatriptan (unless contraindicated for other medical reasons) is best taken by nasal spray or injection as nausea and gastric stasis might well limit the utility of oral administration. The safety of other triptans in pregnancy is less clear.

Partial opioid agonists may be used on a limited basis if the response to other medications is inadequate. Prochlorperazine may help both nausea and headache.

Ergot-containing preparations should be avoided because of possible teratogenicity and the effect this drug may have on the gravid uterus.

Preventive Treatment

Preventive measures can usually be discontinued during pregnancy as migraine tends to improve spontaneously, but they may be required for women who experience frequent, prolonged, and severe attacks that respond poorly to treatment. Patients should avoid known precipitants of attacks, eat regular meals, use relaxation techniques, and maintain good sleep hygiene.

Memantine is well tolerated, appears to be safe during pregnancy, and may be effective for migraine prophylaxis. Propranolol is also effective for migraine prophylaxis but should be avoided during pregnancy when possible or used in the lowest effective dose. This is because animal studies have shown that it may impair fetal growth and that β-adrenergic blockade may inhibit the normal responsiveness of the fetus to asphyxia or other stresses. Other reported complications in neonates include prematurity, respiratory depression, hypoglycemia, and hyperbilirubinemia.[8]

Topiramate and valproic acid, which are effective for migraine prophylaxis, are not recommended during pregnancy because of their teratogenic effects, discussed in an earlier section.

The tricyclic antidepressant amitriptyline is sometimes used in low dose (25–50 mg daily) and seems to be safe during pregnancy. It is best discontinued during the third trimester because of possible effects on the fetus (respiratory distress, drowsiness, hypoglycemia).

Many women, often with a past or family history of migraine, experience mild bifrontal headaches in the week after delivery, sometimes accompanied by photophobia, nausea, and anorexia. These headaches usually respond to simple analgesics or to sumatriptan and settle spontaneously.

Treatment During Lactation

Acetaminophen, NSAIDs (especially ibuprofen), and sumatriptan can be used safely during lactation.

TUMORS

Although any type of intracranial tumor occasionally presents during pregnancy, pituitary adenomas, meningiomas, neurofibromas, hemangioblastomas, and certain vascular malformations sometimes exhibit relapses during pregnancy, with partial or complete remission occurring after delivery. The basis of this relationship is unclear, but it seems likely that pregnancy produces a slight increase in tumor size. The enlargement of certain pituitary adenomas during pregnancy may be due to the trophic effects of increased circulating estradiol. Similarly, an increase in size of meningiomas may relate to a direct trophic effect of gonadal hormones on tumor cells; sex steroid–binding sites have been found in human meningiomas, but there are marked differences in their reported prevalence and concentration. Tumors with symptoms that show a consistent temporal relationship to pregnancy are usually so situated that significant neurologic involvement, with the development of new symptoms or signs, occurs with only slight expansion of the underlying lesion. Thus, spinal meningiomas are more likely than convexity meningiomas to show a relationship of symptoms to pregnancy. Visual field defects are unlikely to develop during pregnancy in patients with pituitary microadenomas, but may certainly occur with larger tumors.

Patients with suspected intracranial neoplasms should be managed during pregnancy as at other times. MRI is generally the best noninvasive means of establishing the diagnosis and does not involve exposing the fetus to irradiation. Essential operative treatment should not be delayed. However, surgery for pituitary adenomas or other benign tumors diagnosed toward the end of pregnancy can often be delayed until after delivery, provided that the patient is followed closely. Radiation therapy or chemotherapy may be required during pregnancy. Radiation therapy is associated with a risk of fetal loss or teratogenicity depending on the level of fetal exposure, especially if administered during the first trimester; in later pregnancy it carries an increased risk of childhood cancer or leukemia. However, tumors of the brain or head and neck can usually be irradiated satisfactorily without dangerous fetal exposure. Therapeutic abortion may need to be considered in some patients with malignant brain tumors, depending on the therapy required and especially when it cannot be delayed to the latter half of pregnancy or postponed until after delivery, or when significant symptoms, such as uncontrollable seizures, complicate the pregnancy.

The pregnancy itself can usually be managed normally in patients with intracranial tumors. Concerns that vaginal delivery may exacerbate any existing increase in intracranial pressure due to the tumor are usually misplaced, especially if adequate regional anesthesia is employed and low forceps are used, if necessary, to shorten the second stage of labor.

The long survival associated with low-grade gliomas suggests that some women with such tumors may wish to become pregnant after the diagnosis has been established. Such decisions need to be made on an individual basis, but patients with these lesions may certainly go through pregnancy without further complications.

Choriocarcinoma may develop after a normal pregnancy or follow a molar, ectopic, or terminated pregnancy. Intracranial metastases are common, and hemorrhage may occur into the cerebral lesions. Early diagnosis and treatment are important for survival.

IDIOPATHIC INTRACRANIAL HYPERTENSION

Idiopathic intracranial hypertension has a clear association with pregnancy and is especially likely to occur during the first trimester or postpartum. It therefore seems sensible that women with this disorder should defer pregnancy until their disease is controlled and important that all pregnant patients with new-onset headaches be examined funduscopically to exclude the diagnosis. Headache and visual disturbances due to papilledema may be accompanied by diplopia from sixth nerve palsy. Investigations reveal no space-occupying lesion, but the cerebrospinal fluid (CSF) pressure is increased. The disorder is self-limiting, but it may not remit for weeks after delivery, and there may be recurrences during subsequent pregnancies. Treatment, as in the nonpregnant woman, consists of measures to lower the intracranial pressure to prevent secondary optic atrophy. It may require the use of acetazolamide, furosemide, corticosteroids, repeated lumbar punctures, or a surgical shunting procedure. Topiramate is also effective but should be avoided during pregnancy. Optic nerve decompression and early delivery of the fetus may have to be considered if the intracranial pressure remains high despite these measures. There are no specific obstetric complications, and a normal birth can be expected.

Intracranial venous sinus thrombosis may simulate pseudotumor cerebri and is discussed later.

CEREBROVASCULAR DISEASE

A significant number of pregnancy-related maternal deaths result from stroke. An increased incidence of stroke has been associated particularly with the puerperium. The highest risk for thrombotic stroke is in the first 6 weeks postpartum and this probably relates at least in part to various hormonal changes.

Sex steroids can affect several physiologic and metabolic factors that predispose to cerebral thromboembolic or venous infarction, as discussed in Chapter 20. The association of stroke with oral contraceptives is well recognized. Estrogens increase blood coagulability and platelet aggregation. Sex hormones may also predispose to aneurysm formation or rupture, as suggested by observations that early menarche or oral contraceptive use is associated with an increased risk of subarachnoid hemorrhage, that the risk of hemorrhage is greatest in the perimenstrual period, and that premenopausal women are at reduced risk of subarachnoid hemorrhage. Whether pregnancy influences intracranial arteriovenous malformations (AVMs) is unclear, but it may certainly aggravate spinal arteriovenous fistulas (p. 587). Eclampsia or pre-eclampsia is the most common cause of stroke during pregnancy, and the microangiopathic syndromes of pre-eclampsia, thrombotic thrombocytopenic purpura, and hemolytic-uremic syndrome are considered on p. 599 and in Chapter 25.

Occlusive Arterial Disease

Most cases of nonhemorrhagic hemiplegia developing during pregnancy or the postpartum period are due to arterial occlusion. As in nonpregnant patients, this may relate to thrombus formation on an atheromatous plaque; inflammatory disorders such as arteritis or meningovascular syphilis; hematologic disorders such as polycythemia and sickle cell disease; and cardiac disorders such as a cardiomyopathy, rheumatic or ischemic heart disease, intracardiac shunts, cardiac dysrhythmias, subacute bacterial endocarditis, use of prosthetic heart valves, and cardiac myxoma. It may be associated with diabetes, cigarette smoking, and migrainous headaches. During pregnancy, in addition, stroke may be predisposed to by anemia, hormonal factors, changes in blood coagulation factors (see Chapter 25), increased platelet aggregation, hypertension, and puerperal septicemia, and by pre-eclampsia or eclampsia (discussed later).

A variety of cardiovascular changes occur during pregnancy: plasma volume increases, a hemodilutional anemia develops, and there is a progressive increase in heart rate and cardiac output as pregnancy advances. The blood pressure declines, however, as systemic vascular resistance drops in early pregnancy, reaching a nadir at around the end of the second trimester. There is thus a relative venous stasis that is enhanced by compression of the inferior vena cava by the enlarging uterus and by diminished physical activity in late pregnancy and the postpartum period. These circulatory changes may bear in part on the development of stroke.

The blood is in a hypercoagulable state during pregnancy; there is a rise in all procoagulant factors except XI and XIII, and increased thrombin activity. Circulating inhibitors of coagulation, such as protein C and protein S, are reduced during normal pregnancy, and antithrombin III may be reduced, as is discussed in Chapter 25. The activity of the fibrinolytic system is also reduced during pregnancy. These various changes predispose pregnant women to stroke. Hemoglobinopathies may also lead to significant maternal morbidity during pregnancy. Thus, women with sickle cell disease are especially likely to experience crises, usually vaso-occlusive, during pregnancy. Sickle cell disease is also associated with an increased incidence of obstetric complication—including abortion, growth retardation, preterm birth, fetal anomalies, pre-eclampsia, eclampsia, and stillbirth—although fetal wastage has been reduced considerably by improved prenatal care.

The presence of circulating antiphospholipid autoantibodies (discussed in Chapters 11 and 25) is similarly associated with a high rate of maternal arterial and venous thrombotic events and transient ischemic attacks (TIAs), as well as with obstetric complications such as an increased rate of spontaneous abortion and of early-onset, atypical pre-eclampsia. Pregnancy may represent an especially high risk of thromboembolic disease in patients with these antibodies. Treatment recommendations are limited by a lack of clinical evidence but may involve low-dose aspirin, unfractionated heparin, or low-molecular-weight heparin.

Hypertensive disorders of pregnancy are associated with ischemic stroke. These disorders include gestational hypertension, which typically resolves within 3 months after delivery, pre-eclampsia and eclampsia, and the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets). Hypertensive disorders of pregnancy are more common in African-Americans than in other segments of the population, and are associated with a significant number of deaths, particularly in developing countries. They are associated with an increased incidence of premature births and stillbirths.

A peripartum cardiomyopathy may occur during the last trimester of pregnancy or the puerperium, especially in the presence of twinning, toxemia, or postpartum hypertension; it sometimes presents with embolic phenomena necessitating anticoagulation. Its precise cause is unclear, but nutritional, hormonal, viral, and immunologic mechanisms have been suggested.[9] Subsequent pregnancies are associated with a significant reduction in left ventricular function and may lead to clinical deterioration and death.[10]

A reversible cerebral vasoconstriction syndrome may occur during an otherwise normal pregnancy or the postpartum period (postpartum cerebral angiopathy) and lead to a fatal outcome.[11] It has been associated with hypertension and use of vasoconstrictive drugs and may be mistaken for cerebral vasculitis. Presentation is commonly with thunderclap headache; focal deficits and seizures may also occur. Cerebral infarction, intracranial bleeding, or vasogenic edema may be associated. The disorder follows a self-limiting course. Treatment is with calcium-channel blockers, but benefit is uncertain. The outcome is variable; full recovery occurs in many patients, but in others the disorder has a fulminant course and may have a fatal outcome or lead to residual deficits.[11]

A reversible intimal hyperplasia of the cerebral vasculature during pregnancy has been described as a rare cause of stroke or TIA during the gestational period, but such cases are poorly documented and hard to interpret. There are rare reports of arterial occlusion by paradoxical embolization from a pelvic vein through a patent foramen ovale. Fat, air, or amniotic fluid embolism may also occur during childbirth but usually presents with dyspnea, shock, and acute encephalopathy. Amniotic fluid embolism is an important cause of stroke and maternal death. Hemodynamic collapse and disseminated intravascular coagulopathy may lead to focal neurologic signs from cerebral hypoperfusion or hemorrhage.

As in nonpregnant women, transient cerebral ischemic attacks may precede occlusion of one of the major intracranial arteries. Neurologic investigation and management should not be influenced by the pregnancy, but special shielding during radiologic studies may help to protect the developing fetus. MRI is the imaging procedure of choice. MR angiography can help to define the vasculature, and diffusion-weighted imaging to detect acute cerebral ischemia. However, gadolinium contrast should not be used if possible—it passes into the placenta and may be harmful to the fetus.

Treatment of thrombotic stroke with tissue plasminogen activator (tPA) is contraindicated during pregnancy and the postpartum period, because safety and efficacy have not been established in these circumstances, but tPA does not cross the placenta, is not teratogenic in animal models, and has not caused problems in published case reports. Hemorrhagic complications are more likely, especially in the first few days after delivery. Angiographic delineation of degenerative atherosclerotic disease in a localized arterial segment that is surgically accessible may permit disobliterative surgery, especially when stenosis is severe (70 to 99% in the internal carotid artery). If surgery is decided against or there is more widespread atherosclerotic disease, treatment is with low-dose aspirin. A cardiac source of emboli usually necessitates treatment with warfarin (as also do certain hypercoagulable states or venous occlusive disease). This drug is associated with risks of teratogenicity and fetal wastage when used during the first trimester, and it crosses the placenta, thereby increasing the risk of hemorrhagic complications. The newer direct-acting anticoagulants also cross the placenta and there is little information on their safety during pregnancy and lactation. Accordingly, patients requiring anticoagulation during pregnancy are best maintained on subcutaneous heparin, which is discontinued with the onset of labor and restarted approximately 12 hours after vaginal delivery (or 24 hours after cesarean section). Hypertension may require treatment (e.g., with nifedipine or methyldopa). Statin drugs are best avoided during pregnancy and lactation.

The optimal management of labor and delivery in patients who have had a stroke during pregnancy is unclear. In most cases, vaginal delivery assisted by forceps is probably satisfactory. The blood pressure needs to be monitored closely, however, to avoid excessively high or low levels.

Occlusive Venous Disease

Aseptic intracranial venous thrombosis may occur during pregnancy, during the puerperium, or with the use of oral contraceptives for reasons that are unclear. It has been attributed to coagulation abnormalities, changes in the constituents of peripheral blood, and intimal damage to dural sinuses (see Chapter 25). The extent to which it relates to hormonal changes is unknown, but such changes probably have an important etiologic role, as discussed in Chapters 11 and 20. In many instances there is no evidence of thrombosis in the pelvic or leg veins. Inherited prothrombotic states associated with intracranial venous thrombosis include protein C, protein S, antithrombin III, and factor V Leiden deficiency, and hyperhomocyteinemia (see Chapter 25); the antiphospholipid antibody syndrome and systemic malignancy may also be associated, and thus require exclusion.[12]

Intracranial venous thrombosis (Fig. 31-1) occurs most commonly during the third trimester of pregnancy or the postpartum period, sometimes in relation to preeclampsia. Although it may, in fact, occur at any time during a normal pregnancy, when it develops during the first trimester it usually is in relation to some complication such as spontaneous or therapeutic abortion. It is characterized clinically by headache, seizures, obtundation, confusion, and sometimes focal neurologic disturbances. Examination commonly reveals papilledema, and there may be signs of meningeal irritation from subarachnoid bleeding secondary to cortical infarction and of focal or multifocal deficits. CSF pressure is often increased, and its protein or cell content may be increased. Imaging procedures, particularly MRI and MR

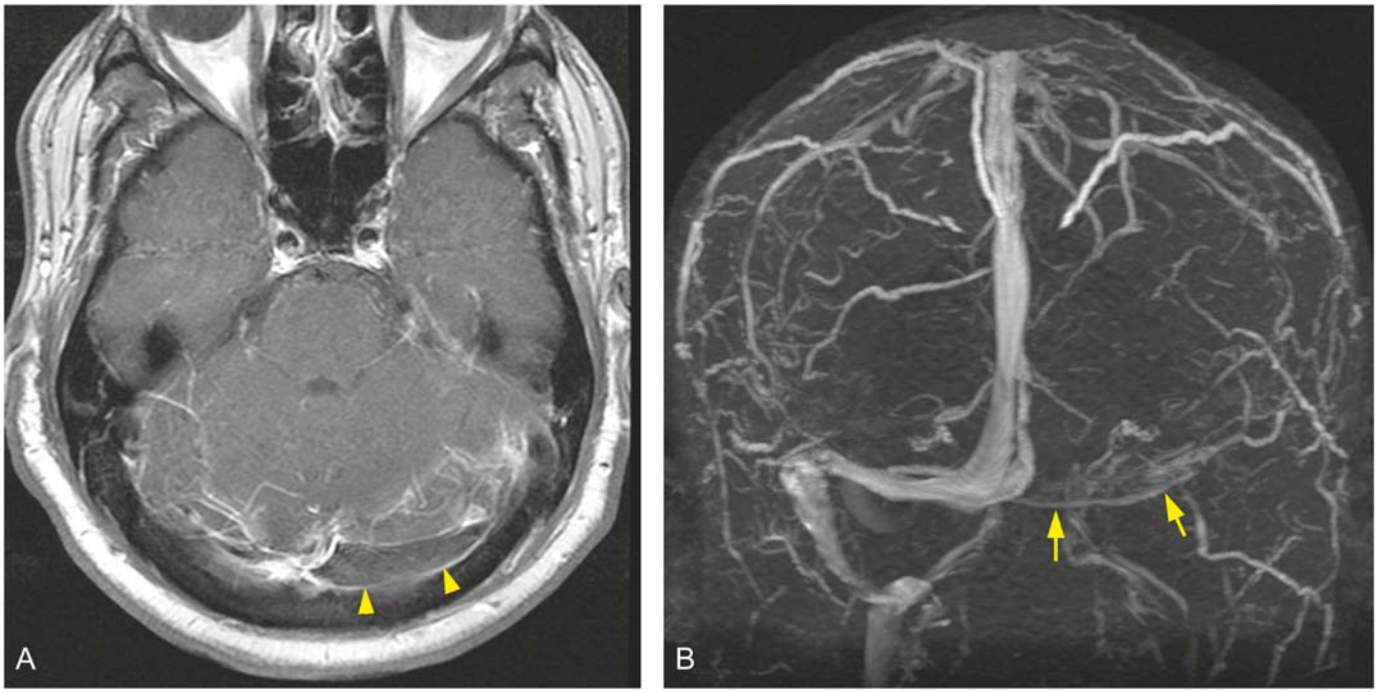

FIGURE 31-1 ■ Thrombosis of the left transverse sinus. *A*, Axial postcontrast T1-weighted MR image shows a filling defect within the left transverse sinus consistent with thrombosis *(arrowheads)*. *B*, Coronal MR venogram confirms thrombosis of the left transverse sinus *(arrows)*. (Courtesy of William P. Dillon, MD, University of California, San Francisco.)

venography or computed tomography (CT) and CT venography, confirm the diagnosisand help to exclude arterial disease.

Treatment of intracranial venous thrombosis is controversial. Anticonvulsant drugs and antiedema agents may be helpful. Anticoagulation with subcutaneous low-molecular-weight heparin is worthwhile despite the risk of provoking hemorrhagic complications and should be continued for the remainder of the pregnancy and the puerperium, followed by anticoagulation with warfarin for at least 3 to 6 months. The heparin is discontinued 24 hours before induction of labor or cesarean section, or with the onset of spontaneous labor, and restarted approximately 12 hours after vaginal delivery or 24 hours after cesarean section. (Many obstetricians replace low-molecular-weight heparin with unfractionated heparin at 36 to 37 weeks, or earlier if preterm delivery is likely because of obstetric complications.) The role of thrombolytic therapy to prevent extension of the thrombus in pregnant or postpartum women is not clear. Different mortality rates have been reported in various series, but a rate of 15 percent is based on the pooled outcomes in a number of studies.[12] Survivors may experience recurrence of thrombosis in subsequent pregnancies. Accordingly, prophylactic low-molecular-weight heparin should be given throughout subsequent pregnancies and the puerperium.

Cesarean section may be necessary if venous thrombosis has occurred before or during labor. If it occurs early in the pregnancy, labor can generally be allowed to commence spontaneously, with forceps-assisted delivery if necessary.

Women with a previous cerebral venous thrombosis should avoid contraceptives containing estrogens.

Pituitary Infarction or Hemorrhage

Acute infarction or hemorrhage of the pituitary gland, especially around the time of delivery, is a well-recognized complication that leads to hypopituitarism if the patient survives the acute event. The disorder may occur in patients with pre-existing diabetes or in those who experience such obstetric complications as postpartum hemorrhage with vascular collapse. It may also occur in patients with coagulopathies or a pituitary adenoma. The extent of pituitary damage governs the severity of pituitary hypofunction. The initial symptom may be failure of lactation. Emergency treatment with corticosteroids and trans-sphenoidal decompression of the intrasellar content may need to be considered to preserve life and vision. Management otherwise is with hormone replacement therapy.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) may occur in patients with a variety of obstetric complications. It is discussed in detail in Chapter 25 and further consideration here is unnecessary.

Subarachnoid Hemorrhage from Intracranial Vascular Anomalies

Subarachnoid hemorrhage may occur during pregnancy from an aneurysm or cerebral AVM (Fig. 31-2). The morbidity and mortality rates are greater with the former. It is unclear whether intracranial AVMs are

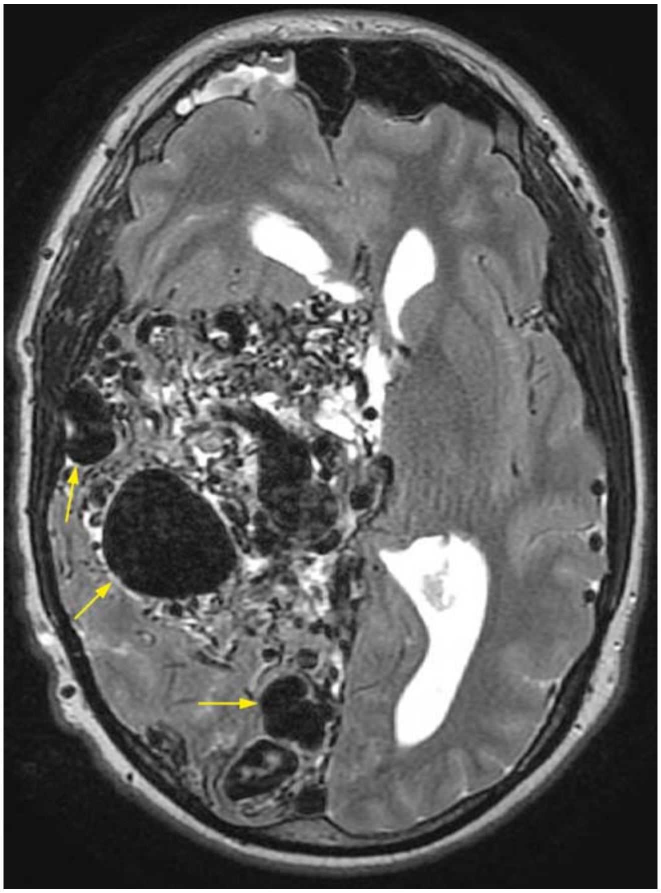

FIGURE 31-2 ■ Axial T2-weighted MR scan showing a large mass of flow voids involving the thalamus, typical of an arteriovenous malformation. The large flow voids *(arrows)* are venous varices, indicating possible outflow obstruction and increased risk of hemorrhage. Midline shift of the lateral ventricle is evident. (Courtesy of William P. Dillon, MD, University of California, San Francisco.)

more likely to bleed during pregnancy, but recent data suggest otherwise.

Symptoms and signs of subarachnoid hemorrhage are as in nonpregnant patients. The hemorrhage may be the first indication of the underlying lesion. An AVM is somewhat more likely than an aneurysm to be responsible if subarachnoid hemorrhage is accompanied by a major focal neurologic deficit (suggesting an intracerebral hematoma). CT scan or MRI of the head detects subarachnoid or intracerebral bleeding and may permit the causal lesion to be identified and localized but, as mentioned earlier, gadolinium contrast should be avoided if possible. Arteriography confirms the identity of the lesion and provides information about its anatomic characteristics that is especially important in planning operative treatment. All of the major intracranial vessels should be opacified because feeders to AVMs sometimes arise from the contralateral side and aneurysms may be multiple. Special shielding during radiologic studies is necessary for pregnant women to protect the developing fetus.

The management of subarachnoid hemorrhage is as for nonpregnant women. Because of the high risk of rebleeding in survivors of a ruptured aneurysm, operative or endovascular treatment should not be delayed because of pregnancy if the clinical and arteriographic findings indicate its feasibility. Treatment of stable unruptured aneurysms can usually be delayed until after childbirth, but enlarging unruptured aneurysms may require more immediate management. Although ruptured AVMs may also bleed again, this may not be for months or years after the initial hemorrhage, and neurosurgical treatment can often be postponed until the pregnancy is over.

The obstetric management of survivors of a subarachnoid hemorrhage is controversial. In patients with aneurysms that have been successfully treated by surgery or in whom rupture occurred before the last trimester, pregnancy and delivery can generally be permitted to continue normally. In patients with unoperated or incompletely obliterated aneurysms that ruptured during the last trimester of pregnancy, either instrumental delivery with regional anesthesia or cesarean section at 38 weeks' gestation is appropriate, depending on obstetric considerations. Some have suggested delivery by cesarean section at 38 weeks for women with AVMs, but this measure seems difficult to justify.

Intracranial hemorrhage during pregnancy or the postpartum period may also occur in association with eclampsia or pre-eclampsia, hypertension, vasculitis, various hematologic disorders, mycotic aneurysms, cocaine abuse, and moyamoya disease and as a manifestation of choriocarcinoma. Treatment is of the underlying cause.

The relationship of oral contraceptive use to intracranial hemorrhage is considered in Chapter 20.

Intracranial Dural Arteriovenous Fistulas

Dural arteriovenous fistulas may present during pregnancy, after abortion, or during the postpartum period. Some are developmental anomalies, but others are acquired in adult life, occasionally following trauma. The anomalous arteriovenous shunt may involve either the anterior-inferior group of dural sinuses (cavernous, intercavernous, sphenoparietal, superior and inferior petrosal, and basilar plexus) or the superior-posterior group (superior and inferior sagittal, straight, transverse, sigmoid, and occipital). Anomalies involving the former group lead typically to unilateral orbital or head pain, diplopia, a proptosed or red eye, tinnitus, or some combination of these symptoms. Malformations involving the superior-posterior dural sinuses may lead to subarachnoid hemorrhage, increased intracranial pressure, tinnitus, seizures, or focal neurologic deficits due to cerebral ischemia. In either case, there may be papilledema, and a bruit is often present either over the eye (with involvement of the anterior-inferior sinuses) or about the mastoid region or ear (superior-posterior sinuses involved).

Arteriography is necessary to localize the shunt with certainty and determine its anatomic features. With shunts to the anterior-inferior dural sinuses, embolization of feeding vessels may help preserve vision or relieve intolerable symptoms. Ligation or embolization of feeding vessels is often helpful in relieving symptoms from shunts to the superior-posterior dural sinuses, and a direct surgical approach is also sometimes feasible.

Spinal Arteriovenous Fistulas and Malformations

Spinal fistulas and AVMs are usually either dural or intradural in location. They may lead to spinal subarachnoid hemorrhage or to a myeloradiculopathy that can either present acutely or develop insidiously. Symptoms usually are progressive. At least one-half of the survivors of subarachnoid hemorrhage from these spinal lesions have further episodes of bleeding, and one-half of the subsequent survivors bleed again unless the underlying lesion is treated. Similarly, once there is any functional impairment in the legs due to the myeloradiculopathy, disability is likely to worsen, so that 50 percent of patients become unable to walk at all or require two sticks or crutches to do so, within 3 years. Spinal cord or root symptoms may show a characteristic relationship to exercise or posture and occasionally to pregnancy or the menstrual cycle.

Typically, examination reveals a mixed upper and lower motor neuron deficit in the legs, often with an associated sensory disturbance that occasionally has a radicular distribution. There may be a co-existing cutaneous malformation that sometimes relates segmentally to the spinal lesion. A spinal bruit may be present.

Unruptured dural arteriovenous fistulas and spinal AVMs probably produce symptoms by causing venous hypertension. Although they are usually extramedullary, their draining veins connect with veins draining the spinal cord. The increased venous pressure leads to a reduction in the arteriovenous pressure gradient across the cord and thus to a reduction in spinal blood-flow. Pressure on pelvic or abdominal veins by the gravid uterus could aggravate symptoms of caudally situated dural arteriovenous fistulas and AVMs by obstructing venous return to the heart, thereby reducing still more the arteriovenous pressure gradient across the cord. Whether anemia and hemodilution are also partly responsible for exacerbations of symptoms during pregnancy is unclear, and it is not known whether sex hormones exert direct trophic influences on these lesions.

Advances in imaging procedures have revealed that the nidus of many spinal vascular lesions is situated durally. Spinal MRI is an excellent screening procedure (Fig. 31-3); if the findings suggest an arteriovenous fistula, spinal angiography is performed to determine its anatomy, the anatomy of the spinal circulation, and the precise level of the abnormal fistula. Treatment of dural lesions is indicated in patients with progressive symptoms, functional incapacity, or a history of hemorrhage, and consists of embolization, surgical excision, or both. Treatment is clearly more difficult for vascular anomalies located anteriorly or within the spinal cord, but in some of these, also, the actual nidus of the lesion is dural and thus operable.

INFECTIONS

A variety of organisms may infect the nervous system, as discussed in later chapters. Pregnancy may interfere with resistance to specific infectious agents, thereby endangering maternal health. Treatment of various infections may also be complicated during pregnancy because of the need to avoid certain antimicrobial agents if possible. When infection occurs during pregnancy, it may pose risks to the developing fetus from the infective organism and the drugs used in its treatment. Obstetric management may be complicated.

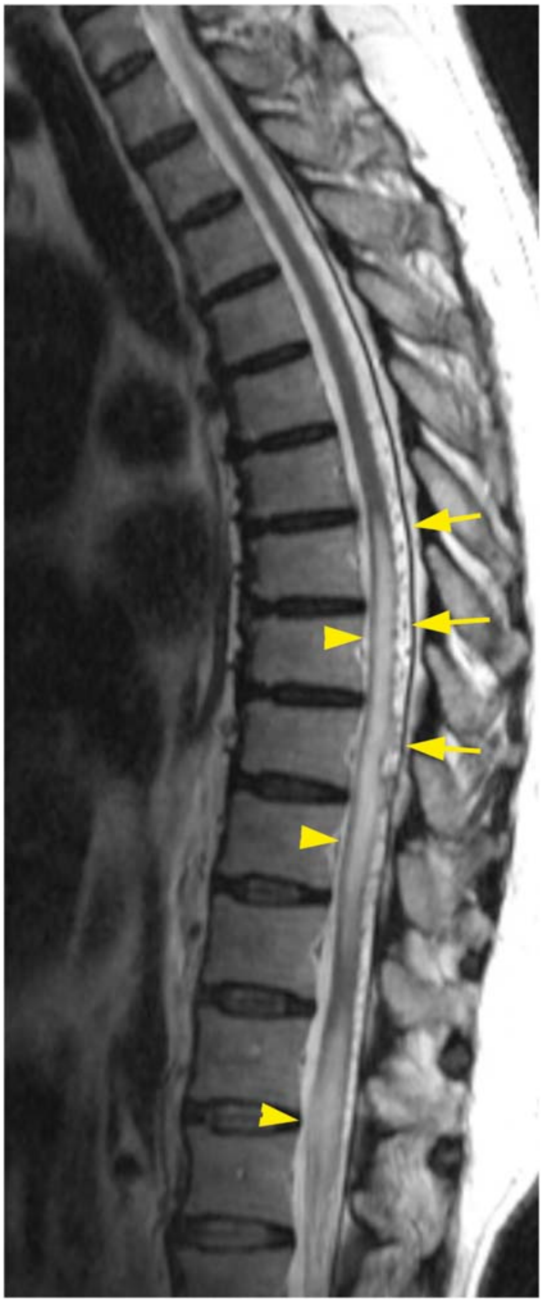

FIGURE 31-3 ■ Sagittal T2-weighted MR scan of the thoracic spine illustrates edema of the central spinal cord *(arrowheads)* and enlarged flow voids posteriorly *(arrows)*. The findings are typical of a spinal dural arteriovenous fistula. (Courtesy of William P. Dillon, MD, University of California, San Francisco.)

Retroviral Infections

Children born to women with *acquired immunodeficiency syndrome* (AIDS) are at risk of developing the disease after an interval that varies from several months to several years. Those infected transplacentally with human immunodeficiency virus (HIV) may be born with congenital AIDS. Infection with HIV may occur not during fetal development but at birth or from breast milk. Neurologic manifestations are particularly frequent in infected children and are due to a progressive encephalopathy that leads to developmental delay or regression, with evidence of cortical atrophy on neuroimaging studies. Calcification of the basal ganglia also occurs. Other manifestations of the disease include failure to thrive, interstitial pneumonitis, hepatosplenomegaly, and increased susceptibility to bacterial infections. Secondary opportunistic infections of the immunocompromised mother are potentially a risk to the fetus or child.

The availability of effective antiretroviral agents and access to infant formula (to prevent postnatal transmission through breast milk) have reduced the incidence of perinatal infections with HIV in developed countries. Combination antiretroviral therapy of infected pregnant women (regardless of CD4 cell count) and nevirapine therapy with or without zidovudine for 6 or 12 weeks for neonates (depending on the infant's risk of infection and method of feeding) are helpful in preventing mother-to-child transmission without an increase in fetal adverse events. Compared with no antiretroviral treatment or monotherapy, combination therapy does not seem to be associated with increased risks of prematurity or other adverse outcomes of pregnancy.

Management of delivery is based on obstetric considerations alone in patients with a low viral load (<1,000 copies/mL) and receiving combination antiretroviral therapy. Cesarean section at 38 weeks to reduce the risk of fetal infection is often preferred for those with higher viral loads or who are untreated.

Because some of the antiviral agents used to treat HIV infection may be teratogenic (in many instances no pharmacokinetic or safety data related to pregnancy are available), infants born of mothers treated with them during pregnancy may theoretically have nervous system abnormalities from the virus itself, from the medications used in its treatment, or both. The virus invades endothelial cells, causes a vasculitis, and leads to microinfarcts in the fetal brain; its effects depend upon the developmental stage of the fetus when it is exposed to the virus, but even late gestational exposures may affect brain development.

Children of women infected with *human T-cell leukemia virus*, type I (HTLV-I) may acquire the infection through breast-feeding and develop a resulting myelopathy in adult life. This is considered further in Chapter 43.

Poliomyelitis

Pregnancy increases the susceptibility of women to clinical poliomyelitis, but it is not clear whether this is because pregnant women are more susceptible to the initial viral infection or to invasion of the nervous system. Weakness tends to be more severe and widespread when poliomyelitis develops during the late stages of pregnancy. Poliomyelitis affects the course of pregnancy. During the first trimester, spontaneous abortion may occur with apparently mild nonparalytic attacks of the disease or in conjunction with a febrile reaction in its acute phase. Abortion or fetal loss may also occur during later stages of pregnancy, but usually in conjunction with severe poliomyelitis. Successful pregnancy may occur, however, even in patients who are dependent on continuous noninvasive positive-pressure ventilation. The uterine muscle is not paralyzed in women with poliomyelitis, and labor can usually be managed as in normal women unless there are specific obstetric indications for cesarean section or induction of labor. Normal offspring can be anticipated, although neonatal poliomyelitis may occur. Neonatal involvement within the first 5 days of life is generally assumed to follow transplacental transmission of the virus and is associated with a 50 percent or greater mortality rate.

Tetanus

Tetanus is an important complication of abortion or delivery, especially in developing countries, and is associated with a high mortality rate. In addition to treating the tetanus, any retained products must be evacuated from the uterus, and hysterectomy is sometimes necessary. Neonatal tetanus results from contamination of the umbilical cord, and in some areas the mortality rate is a high (but uncertain and geographically variable) proportion of all births. Infants are usually diagnosed within 10 days; the history is typically that of increased irritability for up to 48 hours, followed by cessation of sucking and crying, accompanied by convulsions and often by fever. Improved maternity facilities and the active immunization of women who are pregnant or of childbearing age are important public health measures to counter this disorder.

Other Infections

Maternal infection with *Listeria monocytogenes* may lead to abortion or stillbirth as well as to a number of other manifestations including meningitis; in neonates it leads to either an early-onset, predominantly septicemic infection or a late-onset, predominantly meningitic or meningoencephalitic infection. The bacteriologic and serologic findings suggest the diagnosis, and treatment is with appropriate antibiotics.

Maternal *rubella*, especially during the first trimester, may lead to congenital fetal malformations. Ocular abnormalities, seizures, mental retardation, deafness, focal neurologic deficits, and other abnormalities, including cardiac anomalies, occur in a variety of combinations. Much more rarely, a panencephalitic illness has been reported during the second decade of life in patients with congenital rubella and leads to pyramidal and extrapyramidal signs, seizures, and dementia. High antibody titers to rubella virus occur in the blood and CSF, and the virus may be isolated from the brain.

Congenital *toxoplasmosis* causes meningoencephalitis, chorioretinitis, obstructive hydrocephalus, and cerebral calcification. Pregnant women should therefore be advised to keep away from cat feces and to avoid ingestion of raw or undercooked meat or eggs.

Fetal infection with *cytomegalovirus* may lead to a variety of somatic manifestations. Neurologic involvement may be manifested by cerebral malformation, microcephaly, mental retardation, seizures, obstructive hydrocephalus, cerebral calcification, deafness, chorioretinitis, or some combination of these disorders.

Neonatal infection with *herpes simplex virus* leads primarily to visceral involvement. When there is neurologic involvement, manifestations may include seizures, irritability, increased intracranial pressure, depressed level of consciousness, and motor deficits.

Maternal *syphilis* is important to recognize and treat. It is associated with an increased rate of spontaneous abortion and increased perinatal mortality. Offspring of affected mothers may have symptomatic congenital syphilis. Infection may also occur at birth if infants come into contact with an infective lesion. The clinical features of congenital neurosyphilis are similar to those of neurosyphilis in adults. They may become apparent at any time after the first few weeks of life, or they can be delayed for several years. Treatment is of the underlying infection, penicillin being the drug of choice. Fetal infection usually occurs in the second half of pregnancy. Thus, treatment at an early stage of pregnancy generally prevents fetal involvement, emphasizing the importance of serologic testing during antenatal care. Details of treatment are provided in Chapter 39.

Tuberculous meningitis may occur during pregnancy and is then associated with higher mortality and neurologic morbidity rates than otherwise. Its treatment is discussed in Chapter 40.

METABOLIC AND TOXIC DISORDERS

In parts of the world where malnutrition is common, many pregnant women have a deficient intake of diverse nutrients including proteins, vitamins, and minerals. The incidence of malformed fetuses is high in this circumstance, but it is generally not possible to recognize the specific deficiency that is responsible. Fetuses exhibit intrauterine growth retardation, and organ development, including that of the brain, is sometimes affected.

Clinical presentation of the neurologic manifestations of *vitamin B_{12} deficiency* (myelopathy, polyneuropathy, mental changes, optic neuropathy) does not differ during pregnancy, but any accompanying megaloblastic anemia may be obscured by folic acid supplements. As in the nonpregnant patient, treatment is with parenteral vitamin B_{12} to arrest progression and correct reversible neurologic deficits. Maternal vitamin B_{12} deficiency during pregnancy may lead to similar deficiency in neonates, exacerbated in breast-fed infants by the reduced content of vitamin B_{12} in maternal milk. Clinically, such infants exhibit apathy, developmental delay or regression, involuntary movements, cutaneous pigmentation, and megaloblastic anemia. Treatment is with vitamin supplementation.

Phenylketonuria, with its autosomal-recessive inheritance, is an important cause of mental retardation. Neonatal screening programs can identify affected infants so they can be treated before intellectual function deteriorates. Affected women have a high rate of spontaneous abortion. Offspring of untreated women have a high incidence of facial dysmorphism, developmental delay, microcephaly, and congenital heart disease. Family planning and preconception counseling are important, as dietary treatment before conception or as soon as possible thereafter may prevent or lessen some of these features. To ensure that the diagnosis is not missed, antenatal screening for maternal phenylketonuria or testing at the first antenatal visit of women with a positive family history, low intelligence of uncertain cause, or a history of microcephalic offspring is justifiable. The homozygous offspring of an affected mother requires a diet low in phenylalanine, but the most appropriate nutritional management of heterozygotes is less certain. In any event, the affected mother should avoid breast-feeding because of the high concentration of phenylalanine in her milk.

Many *toxins* and *drugs* are teratogenic and may affect the developing nervous system. The teratogenic effects of antiepileptic drugs taken during pregnancy were considered earlier. Excessive maternal alcohol intake may lead to the fetal alcohol syndrome, in which intrauterine growth retardation and dysmorphic facies are common, but cerebral abnormalities (cortical changes, hypoplasia or agenesis of the corpus callosum, and microcephaly) may lead to seizures, mental deficiency, and motor deficits. Excessive vitamin A intake early in gestation may be teratogenic (cleft palate, spina bifida). Many other agents that are seemingly innocuous to the mother may affect the fetus, and the topic is too extensive to be reviewed here. Most drugs are not labeled for use in pregnancy, and there are few or no data on human fetal effects at the time of marketing. The use of medication or recreational agents during pregnancy should therefore be as limited as possible.

MOVEMENT DISORDERS

Movement disorders of any type may occur during pregnancy, as at other times. Comment here is restricted to those related more specifically to pregnancy or posing obstetric problems.

Chorea

CHOREA GRAVIDARUM

Chorea gravidarum occurs most often in primigravidas, frequently without evidence of preceding streptococcal infection, as a variant of Sydenham chorea. Approximately two-thirds of patients have a history of chorea or rheumatic fever, and most of the others have signs of rheumatic heart disease. Symptoms usually begin early in pregnancy; they remit after delivery but may recur during subsequent pregnancies. Altered patterns of circulating sex hormones during pregnancy may account for the chorea by their effects on previously damaged basal ganglia (Chapter 20). The chorea improves after delivery or abortion, as sex hormone levels return to prepregnancy values. The prognosis generally relates to cardiac complications, but there are rare case reports of rhabdomyolysis and a fatal outcome. The neurologic disorder generally benefits from bed rest and sedation, and other treatment is usually unnecessary. In the rare circumstance that symptomatic treatment is required after the first trimester, haloperidol is often preferred because of its less severe maternal side effects. The disorder is not an indication for termination of pregnancy, and there are no specific obstetric complications.

OTHER CAUSES OF CHOREA

Chorea developing for the first time during pregnancy does not necessarily represent a variant of Sydenham chorea. Huntington chorea may occasionally present during pregnancy, and chorea may also develop at this time as a result of systemic lupus erythematosus, polycythemia vera rubra, thyrotoxicosis, hypocalcemia, encephalitis, cerebrovascular disease, or Wilson disease, or as a drug-induced reaction. Further discussion is provided in Chapter 58.

Chorea may be induced by oral contraceptives, sometimes in women with pre-existing abnormalities of the basal ganglia. It usually begins approximately 3 months after contraceptives are started, tends to evolve subacutely, may be asymmetric or unilateral, and settles with discontinuation of the causal agent. Its pathophysiologic basis is unknown, but vascular mechanisms, immunologic mechanisms, and a hormone-dependent alteration in central dopaminergic activity have been proposed.

Restless Legs Syndrome

The restless legs syndrome is about three times more prevalent in pregnant than nonpregnant women, usually developing during the latter part of pregnancy. Unpleasant creeping sensations occur in the legs and occasionally the arms, usually at night or during relaxation, leading to a compelling need to move about and to chronic sleep deprivation. The cause is unknown. Neurologic examination reveals no abnormalities. Treatment of co-existing anemia or iron deficiency may improve symptoms, and treatment with low-dose clonazepam (0.25–1 mg before retiring at night) is sometimes worthwhile. Other drugs that may be helpful include carbidopa-levodopa (Sinemet), dopamine agonists, gabapentin, pregabalin, and opiates, but these drugs are usually best avoided during pregnancy. Symptoms generally resolve spontaneously in the first few weeks postpartum but may recur in subsequent pregnancies. When the syndrome develops during pregnancy, it may also recur unrelated to pregnancy in later life.

Dystonia

When acute dystonia develops during pregnancy, the most probable cause is use of a dopamine antagonist antiemetic or neuroleptic, such as metoclopramide. In patients with long-standing dystonia of either the idiopathic or secondary variety, pregnancy sometimes influences the neurologic outcome, but in an unpredictable manner. In occasional patients, dystonia worsens during pregnancy, but in others remission occurs. There are several reports of dystonia occurring without recognizable cause during pregnancy and resolving before delivery or within a few weeks thereafter; the term "dystonia gravidarum" has been used to refer to such cases. Pregnant patients with dystonia should be offered genetic counseling if the disorder has a hereditary basis. The conduct of labor depends on the severity and nature of the abnormal posturing.

Essential Tremor

Essential tremor is a common disorder, but the published data concerning its occurrence and management during pregnancy are limited. Its pharmacologic treatment is best avoided during pregnancy whenever possible, but disabling tremor may require treatment. Propranolol, discussed earlier, may affect fetal growth and blunt the fetal response to asphyxia. Only low levels of propranolol are found in breast milk and are unlikely to cause any adverse effects in breastfed infants. Primidone also was discussed earlier, in relation to epilepsy.

Parkinson Disease

Parkinson disease may develop in women who are still young enough to bear children. The incidence of obstetric complications or fetal defects is not increased. Concerns are sometimes expressed about the possible effects of pregnancy on the neurologic disorder. There is no consistent effect on overall parkinsonian disability, although some patients may show a worsening of their neurologic symptoms despite continuing on pharmacologic treatment. Deterioration may occur at any time or throughout the pregnancy, but whether this reflects the natural progression of the disease, a pregnancy-related alteration in pharmacodynamics, physical or psychologic stress, hormonal changes, or other factors is unclear. The safety of antiparkinsonian medication during pregnancy is also not known, but levodopa has not been associated with teratogenicity, spontaneous abortion, or birth complications.[13] Amantadine should not be prescribed during pregnancy as it is teratogenic.

The extent to which antiparkinsonian medications are secreted in breast milk, and the effect of these medications on infants, is not clear. Patients are therefore advised not to breastfeed while taking antiparkinsonian drugs.

Tourette Syndrome

The tics of Tourette syndrome may complicate pregnancy but are usually not aggravated by pregnancy. Unless the tics are disabling, medication can be reduced or withdrawn during or prior to pregnancy. When tics cause disability, treatment with neuroleptics (haloperidol or pimozide) is best introduced after the first trimester. The limited available evidence suggests that maternal haloperidol in doses up to 10 mg daily produces low levels in milk that usually do not affect the breastfed infant.

Wilson Disease

Untreated Wilson disease, an autosomal-recessive disorder, is associated with a high miscarriage rate, but pregnancy poses no special problems in patients receiving adequate chelation treatment. Penicillamine therapy may be associated with mesenchymal birth defects, but a number of reports document an uneventful pregnancy with birth of a normal infant in patients treated with penicillamine or zinc sulfate.[14]

MULTIPLE SCLEROSIS

The classic, unpredictable relapses and remissions that occur in multiple sclerosis (MS) make it difficult to determine whether pregnancy influences the disorder. However, several epidemiologic studies have suggested that the relapse rate is reduced during pregnancy but increased during the 3 to 6 months immediately after childbirth. The postpartum increase in relapse rate may relate to fatigue, stress, or a reduction in antenatal immunosuppression. Neither pregnancy itself nor the number of pregnancies affects the degree of subsequent neurologic disability. In some studies MS did not seem to influence the course of pregnancy or childbirth, but in others it was associated with smaller babies for age and more frequent deliveries involving the use of forceps, vacuum extractors, or cesarean section than in controls. Obstetric management may need to be modified for women with significant disability (such as severe spasticity), but MS should otherwise not influence the mode of delivery in most instances.

There is uncertainty about the safety and teratogenicity of many of the medications used in MS, especially the newer disease-modifying agents. Discontinuing them during pregnancy, however, may lead to disease activation especially in the puerperium, when the risk of relapse is already increased. There is limited information to guide decision-making. A consensus statement outlining the position of the Association of British Neurologist has attempted to clarify some of the issues. It urges that at or soon after diagnosis, all women with MS of childbearing age should have prepregnancy counseling, repeated at regular intervals. Patients considering pregnancy should discuss this with their physician before trying to conceive, and the safety of all drug treatments during pregnancy should be reviewed. Disease-modifying drug treatment does not need to be deferred because of a wish to have children. Any relapses during pregnancy or the puerperium can be treated with corticosteroids. The following comments are based largely on those of the UK Consensus Statement.[15]

Glatiramer acetate can be used safely throughout the pregnancy. β-Interferon preparations are probably safe when taken throughout the pregnancy—there is no evidence of fetal teratogenicity. Patients receiving β-interferon therapy when they became pregnant had a higher rate of fetal wastage (miscarriages or stillbirths) and of low-birth-weight babies in some, but not other studies. It has been suggested that patients should stop β-interferon therapy before becoming pregnant; failure to do so, however, does not necessarily imply a bad outcome, and most patients will produce a healthy infant. If stopped during pregnancy, it will take several months for full efficacy to be restored once restarted, so that cover of the puerperium, when the relapse rate is highest, will be incomplete. Thus, the benefits of continuing treatment generally outweigh the risks of treatment.

There may be an increased risk of spontaneous abortion and lower birth weight associated with natalizumab treatment, but it is not clearly teratogenic. Exposure late in pregnancy has been associated with minor, self-limiting hematologic abnormalities in infants. To minimize fetal exposure, it has been suggested that the last dose during pregnancy is given at approximately 34 weeks and the medication restarted soon after birth, ideally within 8 to 12 weeks from the last dose if possible to avoid rebound disease activity.[15] Natalizumab passes into breast milk and the amount increases with time; some therefore advise against breast feeding, despite its advantages and benefits.

There is limited information about the safety of fingolimod in pregnancy and women with MS should be advised to use effective contraception while taking it. Those planning to become pregnant should stop fingolimod at least 2 months before conception and discuss alternative treatments. They should stop fingolimod immediately in the event of an unplanned pregnancy. Pregnancies in women on fingolimod should be treated as high risk and patients referred for a fetal scan. Fingolimod should not be taken while breastfeeding

Teriflunomide is teratogenic in animals at equivalent doses to those given to humans. Women should use effective contraception while taking it and for 2 years after stopping unless they have undergone the accelerated elimination procedure. Those wishing to conceive should switch to another disease-modifying drug, stop teriflunomide, and undergo an accelerated elimination procedure. They should continue to use contraception for at least 6 weeks after serum drug concentrations are less than 0.02 mg/L on two occasions at least 14 days apart. Women who become pregnant while on teriflunomide should undergo a fetal scan.

There is only limited information about the safety of dimethyl fumarate in pregnancy. Women treated with it should use effective contraception and if they do become pregnant they should only continue treatment if the potential benefit justifies the potential risk to the fetus. If a woman taking dimethyl fumarate wishes to become pregnant, the use of alternative treatments should be discussed.

Ocrelizumab, a monoclonal IgG antibody, crosses the placenta, and fetal exposure is likely if the drug is given during pregnancy. The data regarding the use of ocrelizumab in pregnancy are limited. No B-cell count data have been collected in infants exposed to it, and the potential duration of B-cell depletion in infants is unknown. Accordingly, infants should be monitored for B-cell depletion, and inoculation with live and live-attenuated vaccines should be postponed until the infant's B-cell count has recovered. Breast feeding should be discouraged.

Women with MS should not be treated with alemtuzumab during pregnancy or while breastfeeding. The manufacturers recommend that women use effective contraception for 4 months following a course of alemtuzumab. If pregnancy does occur within a month of treatment, increased obstetric monitoring is advised. For 4 years after a cycle of alemtuzumab, women are at risk of autoimmune thyroid disease, immune thrombocytopenic purpura, and other autoimmune diseases. These may occur during pregnancy and affect both the mother and fetus. The women's obstetric team should be informed of these risks.

Cladribine is teratogenic and, given its potential for serious risk to the fetus, the manufacturers recommend that women using hormonal contraception should also use a barrier method of contraception during cladribine treatment and for at least 4 weeks after the last dose in each treatment year. Women should be advised not to become pregnant for at least 6 months after a course of cladribine.

Pregnant women with MS are often concerned about development of the disease in their offspring. Although MS may indeed show a familial incidence, this association is uncommon and tends to involve siblings rather than different generations, so that firm reassurance can generally be given. Pregnancy and parenthood should not be discouraged unless the patient is incapable of coping with the demands involved. Neurologic management during pregnancy is as at other times, but patients with sphincter disturbances or a paraparesis may pose particular problems. The method of delivery should be guided by obstetric factors alone.

OPTIC NEURITIS

Optic neuritis of any type may occur fortuitously during pregnancy. Optic nerve involvement is a rare complication of hyperemesis gravidarum, and uncontrollable vomiting may necessitate termination of pregnancy. Optic nerve involvement may occur during pregnancy or the postpartum period in patients with MS or tumors that enlarge slightly during the gestational period. Genetic counseling is important if there is a history of hereditary optic atrophy.

TRAUMATIC PARAPLEGIA

When spinal injury occurs during pregnancy, the patient must be investigated and managed with her own best interests in mind. Despite concerns that radiologic studies might affect the developing fetus, such studies should not be postponed if indicated neurologically.

Patients with established paraplegia should be educated about (1) the importance of avoiding urinary infection by ensuring a minimal amount of residual urine after micturition, and (2) the best means of avoiding pressure sores. Unless a paraplegic woman has a gross impairment of renal function, however, she need not be discouraged from pregnancy if she wishes to have a family. Care should be taken to prevent anemia during pregnancy.

The conduct of labor is complicated in paraplegic women. With complete cord lesions above T10, onset of labor is unrecognized and labor is painless. For this reason, the cervix is usually examined at each antenatal visit after approximately the 26th week of pregnancy; patients are hospitalized if the cervix is dilated, or routinely after about 32 weeks of pregnancy. With cord lesions below T10, uterine contractions are accompanied by normal pain sensations.

Complete cord lesions above T5 or T6 may be associated with *autonomic hyperreflexia*. Headache, sweating, nasal congestion, hypertension, reflex bradycardia, and cutaneous vasodilation and piloerection above the level of the lesion are often conspicuous during the uterine contractions of labor, becoming especially marked just before delivery. If unrecognized, the disorder is sometimes mistaken for pre-eclampsia. Symptoms have been attributed to release of catecholamines. Treatment in the past has included reserpine (to deplete catecholamines from sympathetic nerve terminals), atropine, clonidine, glyceryl trinitrate, or hexamethonium. Continuous lumbar epidural anesthesia can block or prevent autonomic hyperreflexia.

Cesarean section is not necessarily indicated by the paraplegia itself but may be required if there is bony deformity of the spine or pelvis. Forceps delivery may be necessary to compensate for paralysis of muscle involved in the expulsive efforts of the second stage or to shorten delivery time because of severe hypertension. Paraplegic and even quadriplegic patients have a normal milk ejection reflex during suckling and can breast-feed their infants.

ROOT AND PLEXUS LESIONS

Low back pain is common during pregnancy. There is usually no serious underlying neurologic cause, so that management is generally conservative. Acute *prolapse of a lumbar intervertebral disc*, for example, is rare during pregnancy and must be distinguished from conditions simulating it. This may require imaging. MRI during pregnancy is without known adverse effects on the fetus, but the use of contrast agents is best avoided if possible. Compressive injuries of the lumbosacral plexus may occur during labor and can be difficult to distinguish from an acutely prolapsed lumbar intervertebral disc. However, disc prolapse is associated with tenderness and rigidity of the lumbar spine, sciatica, and signs of root tension. Electrophysiologic studies may also clarify the diagnosis, depending on whether there is evidence of involvement of the paraspinal muscles (which are supplied proximally from the nerve roots). Management of lumbar disc prolapse during pregnancy is generally conservative, with surgery considered primarily for patients with significant progressive neurologic deficits or cauda equina syndrome. The optimal method of delivery for women with significant lumbar disc herniation is unclear because straining may worsen the herniation; cesarean section is often advocated in this circumstance.

Lumbosacral plexus lesions result from compression by the fetal head or obstetric forceps of the roots of the sciatic nerve. This injury is especially likely when there is minor disproportion or when midforceps are used during delivery because of malpresentation. Anatomic features of the pelvis that predispose to this complication include a straight sacrum; a flat, wide posterior pelvis; posterior displacement of the transverse diameter of the inlet; wide sacroiliac notches; and prominent ischial spines. Symptoms are usually unilateral and develop immediately after delivery. There is often predominant involvement of fibular (peroneal) fibers, as reflected by the distribution of motor and sensory findings. With mild injuries, the prognosis for recovery is excellent, but recovery may be prolonged and incomplete if axonal degeneration has occurred. Electrophysiologic studies therefore assist in determining prognosis. Treatment of severe cases with calipers and a night cast prevents contractures.

Despite an obstetric lumbosacral plexus palsy, delivery in subsequent pregnancies need not be by cesarean section. However, cesarean section is appropriate if the infant is large or there are premonitory symptoms suggesting nerve compression with attempted engagement of the fetal head during the last 4 weeks of pregnancy.

Maternal brachial plexopathy may be idiopathic or occur on a familial basis (also known as hereditary neuralgic amyotrophy). In some of the reported cases there has been a clear association of attacks with pregnancy or the puerperium; inflammation, probably immune-based, appears pathogenic at least in some instances. Pain in the shoulder or arm occurs and may last for several weeks, followed by wasting and weakness of muscles in the affected area. Reflex and sensory changes also occur. Mutations or duplications in the *SEPT9* gene on 17q25, inherited in an autosomal-dominant manner, are involved in many familial cases. A hereditary basis is suggested by recurrent episodes, especially postpartum, a positive family history, involvement of nerves beyond the brachial plexus, and the presence of mild dysmorphic features such as hypotelorism, epicanthic folds, low-set ears, and a small mouth. Early treatment with corticosteroids may be helpful.

PERIPHERAL NERVE DISORDERS

Entrapment Neuropathies

Two entrapment neuropathies are especially likely to occur during pregnancy. *Carpal tunnel syndrome* occurs often, possibly because of fluid retention. Nocturnal pain and paresthesias in the hand disturb sleep. Weakness of the thenar muscles occurs in more advanced cases. The clinical and electrophysiologic features of the disorder do not require description here. When the syndrome develops during pregnancy, it most often does so in the third trimester (although it may present earlier), and typically settles within approximately 3 months of delivery, often within 2 weeks; however, symptoms with onset in early pregnancy are less likely to improve after delivery. Treatment should be conservative. The use of a nocturnal wrist splint is often helpful for alleviating symptoms; the splint should maintain the wrist in a neutral or slightly flexed position. Salt restriction, local injection of corticosteroids into the carpal tunnel, or treatment with diuretics sometimes helps. The patient should be reassured about the benign nature of her symptoms. Surgical division of the anterior carpal ligament is usually unnecessary unless symptoms become intolerable or continue to progress in the weeks after delivery. In some instances, carpal tunnel syndrome develops in the puerperium; it may then relate to the position of the hand and wrist during breast-feeding. Treatment is conservative, but the wearing of wrist splints at such a time may be difficult.

Entrapment of the lateral femoral cutaneous nerve is also common during pregnancy, especially in its later stages, and leads to the syndrome of *meralgia paresthetica.* Pain, paresthesias, and numbness occur about the outer aspect of the thigh, usually unilaterally, and are sometimes relieved by sitting. Clinical examination reveals no abnormality except in advanced cases, when cutaneous sensation may be disturbed in the affected area. Symptoms generally settle spontaneously within a few weeks of delivery, and the patient can therefore be reassured. In rare instances, however, the pain has reportedly been so severe that labor has been induced early. Local injection of hydrocortisone about the region where the nerve lies medial to the anterior superior iliac spine may provide temporary benefit. Symptomatic relief may also follow treatment with low-dose tricyclic antidepressants. Anticonvulsant drugs such as carbamazepine should be avoided during pregnancy. The safety of treatment with lidocaine patches during pregnancy has not been established.

Traumatic Mononeuropathies

A number of isolated nerve lesions may occur as a complication of various obstetric maneuvers. Lower-limb nerve injury has been associated with nulliparity and a prolonged second stage of labor. The *obturator nerve* may be injured when the patient is in the lithotomy position because of angulation as the nerve leaves the obturator foramen. It may also be compressed between the fetal head and the bony pelvic wall. Similarly, an isolated *femoral neuropathy* may occur by angulation and pressure from the inguinal ligament when the thighs are markedly flexed and abducted, as when anesthetized patients are placed in the lithotomy position; stretch of the nerve by excessive hip abduction and external rotation may also occur. The *saphenous nerve* is sometimes injured by pressure from leg braces when the patient is improperly suspended in the lithotomy position. The most common cause of *sciatic nerve* palsy is a misplaced deep intramuscular injection, but this nerve can also be injured by stretch when a patient is placed in stirrups on the obstetric table. To avoid such injury, the knee and hip joints should be well flexed and extreme external rotation of the hip avoided. The *common fibular (peroneal) nerve* may be injured in the region of the head of the fibula by pressure from the leg braces of the obstetric table, especially in anesthetized women. The clinical features of all these neuropathies are well known and are not recapitulated here.

Damage during labor and delivery to the innervation of the sphincter muscles in the pelvic floor may be responsible for stress incontinence of urine or feces, as discussed in Chapter 29.

Bell Palsy

Idiopathic lower motor neuron facial palsy is common and shows a definite association with pregnancy, attributed by some to fluid retention, a viral inflammatory reaction, or pregnancy-related change in immune function. Approximately 85 percent of cases occurred during the third trimester of pregnancy or the puerperium. The onset of Bell palsy during pregnancy has been related to hypertensive disorders, implying that patients who develop Bell palsy during pregnancy should be monitored closely for hypertension or preeclampsia. Diabetes should be excluded. Although most patients with Bell palsy recover completely without treatment, such recovery may be less likely for women with a complete palsy developing during pregnancy than for the general population. Despite questions concerning its efficacy, treatment with corticosteroids is generally prescribed for Bell palsy, especially if a poor prognosis is anticipated because of severe pain or a clinically complete palsy and if patients are seen within the first week of the disorder. However, corticosteroids are perhaps best avoided during the first trimester, at least in those with a good prognosis, because incomplete evidence suggests they may increase the risk of oral clefts. Antiviral therapies are probably not effective. In patients with a complete facial palsy, protection of the cornea should be ensured. Electrodiagnostic evaluation after the first week provides a guide to prognosis.

Polyneuropathies

There is no specific polyneuropathy of pregnancy, but any type may occur during the gestational period. *Nutritional deficiency* is probably the most likely cause in patients from one of the developing nations or in those with hyperemesis. There may be evidence of peripheral nerve involvement in patients with hyperemesis gravidarum complicated by Wernicke encephalopathy and sometimes by Korsakoff syndrome. Diagnosis is confirmed by finding a marked reduction in blood transketolase activity and a marked thiamine pyrophosphate effect. As in nonpregnant women, treatment is with thiamine, 100 mg being given once intravenously and then intramuscularly for several days until a satisfactory diet is ensured. Vitamin B_{12} deficiency was discussed earlier (see p. 590).

Guillain–Barré syndrome may occur during any stage of pregnancy or in the puerperium. It may be associated with antecedent infections such as with *Campylobacter jejuni* or cytomegalovirus. Its course is not influenced by pregnancy. Approximately 3 percent of patients have one or more relapses, sometimes several years after the initial illness, and they occasionally occur in relation to pregnancy. There has been a case reported of a mother with cytomegalovirus-related acute inflammatory neuropathy that developed approximately 10 weeks before delivery of a healthy infant who, in turn, developed a neonatal inflammatory neuropathy after several days.

Serial ultrasonographic fetal monitoring has sometimes been performed but usually reveals normal fetal movement, even when paralysis is severe in the mother. Early ventilatory support may be helpful in preventing fetal hypoxia. Hypotensive episodes due to autonomic involvement may necessitate volume expansion to ensure adequate placental perfusion. The maternal outcome appears unaffected by early delivery. The Guillain–Barré syndrome is treated as in nonpregnant women; experience with plasmapheresis or intravenous immunoglobulin therapy is more limited in this circumstance but both have been used safely during pregnancy. Delivery may require forceps or assisted extraction devices because of weakness of the abdominal muscles, which may reduce the ability to increase the intra-abdominal pressure voluntarily; uterine contractions are normal.

When relapse of *chronic inflammatory demyelinating polyneuropathy occurs* during pregnancy, it is usually late in pregnancy or in the puerperium. There are no specific fetal complications. Treatment is as in nonpregnant women, but concerns regarding plasmapheresis and intravenous immunoglobulin merit reiteration; there is further concern about the use of azathioprine, cyclosporine, and cyclophosphamide, which may retard fetal growth and have other adverse effects, including potential teratogenicity. *Multifocal motor neuropathy* with conduction block may be exacerbated during pregnancy but responds to intravenous immunoglobulin therapy; after pregnancy, power commonly reverts to its previous level.

Pregnancy may lead to acute exacerbations in the hepatic type of *porphyria*. The usual neurologic manifestation is a polyneuropathy that is predominantly motor but sometimes has pronounced autonomic accompaniments. Cerebral manifestations may also occur. In many patients with hepatic porphyria, however, pregnancy is well tolerated. Relapses may occur at any time, but are most likely during early pregnancy and may then lead to spontaneous abortion. Patients with this disorder who are contemplating pregnancy must therefore understand the implications and uncertain outcome, and they must be monitored closely during the gestational period. Caution must also be exercised in the medications used during and after labor because they may provoke exacerbations.

MYASTHENIA GRAVIS

Myasthenia gravis, an autoimmune disorder of neuromuscular transmission, is associated most commonly with antibodies against muscle nicotinic acetylcholine (ACh) receptors; in seronegative cases, antibodies against muscle-specific kinase are often present. Exacerbations of myasthenia gravis may occur in relation to the menstrual period. The disorder may be influenced in an unpredictable manner by pregnancy, and the effect of pregnancy may vary in the same patient on different occasions. Pregnancy does not worsen the long-term outlook. The severity of the myasthenia at the time of the pregnancy does not predict the occurrence of exacerbation or remission. Remission occurs during pregnancy in approximately 30 percent of cases, relapse in between 30 and 50 percent, and no change in the remainder. A significant additional number of relapses occur in the postpartum period, when they tend to be particularly severe; these may relate in part to postpartum infection. Relapses may occur at any time during the pregnancy. Severe relapse of the disorder may suggest the need for termination of pregnancy, but termination does not necessarily lead to clinical benefit. The myasthenia must be treated effectively but, as indicated earlier, the safety (to mother or fetus) of cholinesterase inhibitors, immunosuppressive agents, plasmapheresis, and intravenous immunoglobulins during pregnancy is not completely clear; the potential risks of such treatment, however, must be balanced against the risks to both mother and fetus of myasthenic crisis. Evidence suggests that mycophenolate mofetil is best avoided in pregnancy because it is teratogenic and has been associated with first-trimester pregnancy loss. There have also been concerns about the possible teratogenicity of azathioprine in animal studies, and fetal malformations have occurred in humans that possibly related to the drug. Both plasmapheresis and intravenous immunoglobulin therapy have been used safely and effectively in myasthenic patients during pregnancy.

Myasthenia gravis has little effect on pregnancy itself, unless it leads to maternal respiratory inadequacy; weakness of the respiratory muscles may be exacerbated by a restriction of diaphragmatic excursions by the growing fetus. There is sometimes a marked contrast between the strength of uterine contractions during the second stage of labor and the severity of skeletal muscle weakness. Enemas should not be given because they may precipitate a myasthenic crisis. Cesarean section is best reserved for patients in whom it is indicated for obstetric reasons. Regional anesthesia rather than general anesthesia is desirable, and the use of muscle-relaxant drugs should be avoided if possible. Magnesium sulfate should not be used in myasthenic patients with toxemia because of its effects on neuromuscular transmission. In a population-based cohort study, no significant differences were found in perinatal mortality, mean gestational age, or birth weight between the offspring of myasthenic and nonmyasthenic women.[16] Breast-feeding is not contraindicated.

Neonatal myasthenia, a transient disorder that may relate to placental transfer of maternal antibodies against ACh receptors, occurs in approximately 10 to 15 percent of the newborn infants of myasthenic women, regardless of the duration or severity of the maternal illness or ACh receptor antibody titer. Infants of myasthenic mothers should therefore be watched carefully for clinical signs of the disorder: a poor cry, respiratory difficulties, weakness in sucking, feeble limb movements, and a weak Moro reflex. Symptoms generally become apparent within the first 3 days of birth but are not usually evident immediately after birth. The neonatal disorder can be treated with anticholinesterase drugs if necessary, and it usually subsides within 6 weeks of delivery. Its occurrence in one child does not imply that subsequent children born to the same mother will have the disorder.

The transient neonatal form of myasthenia is distinct from congenital myasthenia, which is rare, occurs in children born to healthy mothers, and is a life-long disorder that varies in type with age of onset, severity, and pathogenesis.

MYOTONIC DYSTROPHY

The weakness and myotonia of myotonic dystrophy type 1 may worsen during pregnancy, and the course of the disorder sometimes appears to accelerate during the gestational period. Women with early-onset myotonic dystrophy are more likely to experience a complicated pregnancy than those with later onset. A number of obstetric complications have been reported, including threatened, spontaneous, and habitual abortion; ectopic pregnancy; preterm labor; and placenta praevia. Perinatal loss (stillbirths or neonatal deaths) is increased and has been related to congenitally affected fetuses and associated complications of the pregnancy. Premature onset of labor in patients with myotonic dystrophy has sometimes been attributed to abnormalities of uterine muscle. The uterus may fail to contract normally during labor, so that the first stage is prolonged, and retention of the placenta and postpartum hemorrhage may occur. Skeletal muscle weakness may also lead to difficulties during the second stage of labor. If anesthesia is required for obstetric reasons, depolarizing muscle-relaxant drugs should be avoided because they may cause myotonic spasm, and nondepolarizing drugs are given in reduced dosage to patients who are taking quinine for their myotonia. Electrocardiographic monitoring facilitates the early recognition of cardiac arrhythmias, to which patients with myotonic dystrophy are prone, and which may require a pacemaker. General anesthetics may lead to marked respiratory depression, and regional analgesia is the preferred method of management.

Type 2 myotonic dystrophy (CCTG expansion in intron 1 of the *ZNF9* gene on chromosome 3q 21.3) may first become manifest during pregnancy, with worsening occurring in subsequent pregnancies, for uncertain reasons. When initial symptoms occur before or during pregnancy, marked improvement often follows delivery, with a recurrence of symptoms in subsequent pregnancies. In one series, preterm labor occurred in 50 percent of pregnancies and was more likely in women who developed the first symptoms or a deterioration of the myotonic dystrophy during pregnancy compared with those in whom an influence of gestation on the disease course was inapparent. No increased obstetric risk was found, and early pregnancy loss rate was normal.[17]

Myotonic dystrophy type 1 (expanded CTG repeat in the *DMPK* gene) may occur congenitally among the offspring of mothers with the disease. An affected mother is more likely to have a child with congenital myotonic dystrophy in a first pregnancy if she has multisystem disease when pregnant, age at onset is less than 30 years, her father is the affected parent, and CTG expansion is more than 1 kb; however, even subclinically affected women with low repeat sizes can have congenitally affected offspring. Recurrence risk to further children is high if an affected woman has given birth to one child with congenital myotonic dystrophy. There may be a history of hydramnios or reduced fetal activity during late pregnancy. Affected infants may die within hours or a few days of birth. Clinical features of the disorder in such infants include facial diplegia, hypotonia, respiratory distress, feeding difficulties, delayed motor development, and mental retardation. Talipes is also common. Myotonia is absent clinically in neonates with the congenital form of myotonic dystrophy but is uniformly present in children 10 years or older. Myotonic dystrophy type 2 has not been reported in congenital form.

In congenital myotonic dystrophy, transmission is generally via the mother. The data suggest that the disorder results from the combination of the gene responsible for the disorder in adults, with some additional maternally transmitted factor.

The gene causing myotonic dystrophy type 1 is on chromosome 19q13.2-q13.3 and has variable penetrance; increasing numbers of triplet repeat expansions govern development of clinical disease. Genetic counseling is an important consideration for women with myotonic dystrophy who are contemplating pregnancy. Counseling and planning of pregnancy may be difficult in patients with mild cognitive impairment or behavioral disturbances. Prenatal detection of the disorder provides the opportunity for abortion of an affected fetus.

ECLAMPSIA AND PRE-ECLAMPSIA

Reference has not been made in this chapter to eclampsia (defined as the occurrence of seizures or coma in a patient with pre-eclampsia, i.e., the onset of hypertension and proteinuria during the second half of pregnancy), which is usually treated by obstetricians rather than neurologists. The neurologic manifestations of pre-eclampsia or eclampsia include headache, tinnitus, diplopia, visual blurring, scotomas, and transient blindness that may arise cortically. The pathophysiologic basis of the seizures or coma that occur in patients with eclampsia is unclear, but the cerebral dysfunction has been attributed to a number of factors, including intensive vasoconstriction, endothelial damage, cerebral edema, and DIC in the cerebral microcirculation. The relationship between hypertension, seizures, and cerebral dysfunction is unclear and unpredictable, but a further increment in the previously elevated blood pressure or an exacerbation of headache may be noted. Imaging (CT scans or MRI) may reveal cerebral edema, ischemia, infarction, or hemorrhage, and angiographic evidence of vasospasm is sometimes found; the radiologic findings resemble those in hypertensive encephalopathy. Treatment generally consists of controlling hypertension, preventing convulsions, and reducing cerebral edema. In extreme cases, termination of pregnancy may be necessary. In general, seizures can be controlled with intravenous diazepam, with the addition of phenytoin if necessary. Many obstetricians prefer to use magnesium sulfate to control eclamptic seizures, and some justification exists for this approach, which may be superior in this context to phenytoin or diazepam. A common regimen is to administer 10 g intramuscularly followed by 5 g intramuscularly every 4 hours, depending on renal output. The aim is to achieve a serum magnesium level of 5 to 8 mEq/L. Other therapeutic approaches reflect obstetric management and include prompt delivery, and need not be recapitulated here. Low-dose aspirin (81 mg/day) after 12 weeks of gestation may reduce the risk of pre-eclampsia in women with a past history of the disorder.

Pre-eclampsia (hypertension, proteinuria, and edema, occurring between the twentieth week of gestation and 48 hours postpartum) may present with a variety of manifestations due to involvement of such different organs as the kidney, liver, heart, central nervous system, or blood-clotting system. It may be clinically impossible to distinguish between pre-eclampsia and either thrombotic thrombocytopenic purpura or the hemolytic-uremic syndrome. Hematologically, however, pre-eclampsia is characterized by DIC and reduction of plasma antithrombin III activity, in contrast to thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome. The so-called HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), probably a variant of pre-eclampsia, frequently has major neurologic consequences such as intracerebral hemorrhage.

The *posterior reversible leukoencephalopathy syndrome* (PRES) is sometimes considered to be indicative of eclampsia, even when there are no other features of eclampsia (proteinuria, hypertension). It is characterized by the gradual onset of headache, confusion or an impairment of consciousness, visual changes, and seizures, associated with edema of the posterior cerebral (parieto-occipital) white matter on imaging studies. The MRI findings consist most often of punctate or confluent areas of increased signal on proton density and T2-weighted images (Fig. 31-4). Treatment is as for pre-eclampsia or eclampsia. PRES also occurs in hypertensive crisis or with cytotoxic immunosuppressive therapy, with acute or chronic renal disease (see Chapter 16), in various vasculitic disorders, hemolytic-uremic syndrome, and thrombotic thrombocytopenic purpura, after organ transplantation, with sepsis, and in many other clinical settings. Treatment is focused on control of the blood pressure.

Thrombotic thrombocytopenic purpura is characterized by fever, Coombs-negative hemolytic anemia, thrombocytopenic purpura, fluctuating neurologic involvement, and renal disease, and it may simulate pre-eclampsia. Its neurologic features are discussed in Chapter 25. Thrombotic thrombocytopenic purpura may develop during the antepartum period, often before approximately 24 weeks of gestation, and may result in infant death, although successful treatment may permit prolongation of the pregnancy. Treatment is by plasma exchange or

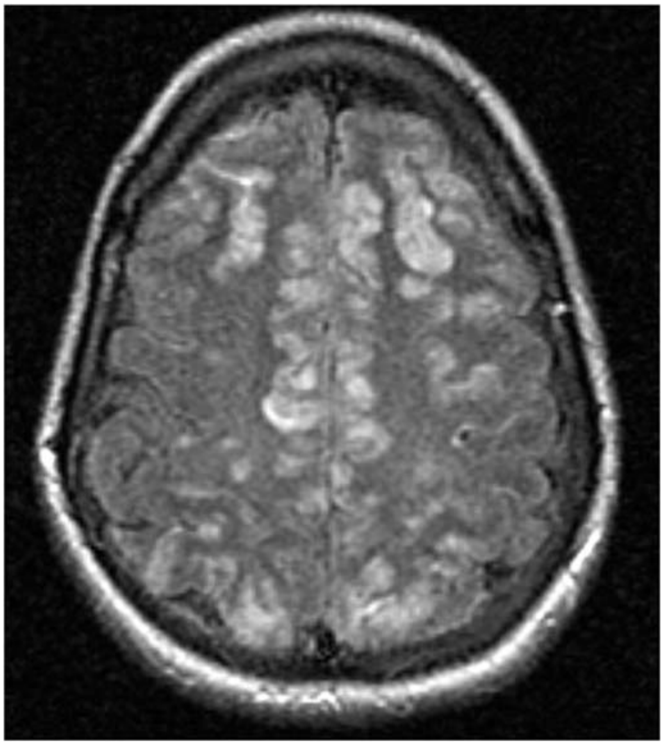

FIGURE 31-4 ■ Posterior reversible leukoencephalopathy syndrome (PRES) in a patient with eclampsia, following a seizure. Axial T2-weighted FLAIR MR image demonstrates symmetric high signal intensity, in this instance involving also the cortex of the frontal and parietal lobes bilaterally. (Courtesy of William P. Dillon, MD, University of California, San Francisco.)

infusion. Platelet transfusions should be avoided because they may trigger an exacerbation. Antiplatelet agents (such as aspirin or dipyridamole) usually are not effective, but treatment with corticosteroids may be helpful. Postpartum *hemolytic-uremic syndrome* is similar to thrombotic thrombocytopenic purpura, and many consider it within the same spectrum.

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SECTION

10

Toxic, Environmental, and Traumatic Disorders

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CHAPTER

32

Drug-Induced Disorders of the Nervous System

FRANK L. MASTAGLIA

HEADACHE
- Vascular Headaches
- Medication Overuse Headache
- Idiopathic Intracranial Hypertension
- Aseptic Meningitis

STROKE

SEIZURES

ENCEPHALOPATHY

DRUG-INDUCED COMA

NEUROPSYCHIATRIC DISORDERS
- Behavioral Toxicity
- Delirium and Confusional States
- Mood Disorders
- Psychoses
- Hallucinatory States
- Cognitive Impairment

MOVEMENT DISORDERS
- Akathisia
- Acute Dystonic-Dyskinetic Reactions
- Tardive Dyskinesia and Other Tardive Syndromes
- Levodopa-Induced Dyskinesias
- Chorea and Choreoathetosis
- Tics
- Myoclonus
- Tremor
- Parkinsonism

CEREBELLAR SYNDROMES

NEUROLEPTIC MALIGNANT SYNDROME

SEROTONIN SYNDROME

OTOTOXICITY

VISUAL DISORDERS
- Pupillary Changes
- Refractive Changes
- Retinopathy
- Optic Neuropathy
- Disorders of Color Vision
- Cortical Blindness
- Diplopia
- Nystagmus

DISORDERS OF TASTE AND SMELL

SPINAL DISORDERS

AUTONOMIC DISORDERS
- Postural Hypotension
- Bladder Dysfunction
- Sexual Dysfunction

PERIPHERAL NEUROPATHIES
- Antineoplastic Drugs
- Antimicrobial Agents
- Antirheumatic Drugs
- Cardiovascular Drugs
- Cholesterol-Lowering Agents
- Hypnotic and Psychotropic Drugs
- Levodopa
- Other Drugs

NEUROMUSCULAR TRANSMISSION DISORDERS

MUSCLE DISORDERS
- Cholesterol-Lowering Agents
- Inflammatory Myopathies
- Acute Rhabdomyolysis
- Mitochondrial Myopathies
- Potassium-Related Myopathies
- Glucocorticoid Myopathy
- Acute Quadriplegic Myopathy
- Autophagic Myopathies
- Malignant Hyperthermia
- Drug-Induced Myotonia
- Myalgia, Cramps, and Twitches
- Other Rare Drug-Induced Myopathies

Adverse drug reactions are a common and important cause of morbidity and hospital admission and are a major burden on the healthcare budget. Drug reactions commonly involve the nervous system, causing a variety of disorders that may be serious and even life-threatening, and may mimic naturally occurring neurologic disorders. Unlike many of these, most drug-induced disorders are readily reversible if the

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offending agent is identified early and withdrawn. It is therefore essential that the possibility of an iatrogenic condition should be considered in any patient presenting with neurologic symptoms, and a full drug history should always be obtained with this in mind. The spectrum of drug-induced disorders is diverse, as discussed in this chapter.

HEADACHE

Drugs can cause headache through a number of different mechanisms, such as by inducing cerebral vasodilation or vasoconstriction, raised intracranial pressure, or aseptic meningitis. Moreover, medication may exacerbate a pre-existing headache disorder such as migraine or tension-vascular headache.

Vascular Headaches

Many drugs cause headaches by inducing vasodilation or reversible cerebral vasoconstriction. These include sympathomimetics, amyl nitrate, nitroglycerin, antihistamines, nicotinic acid, pentoxifylline, nifedipine, theophylline, aminophylline, terbutaline, and dipyridamole. Headache may also occur during treatment with cyclosporine, bromocriptine, dopamine, and nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., naproxen, ketoprofen, diclofenac, alclofenac, ibuprofen), and in patients taking H_2-receptor antagonists (e.g., cimetidine and ranitidine) and proton pump inhibitors (e.g., omeprazole and lansoprazole).

Headache is common during intravenous immunoglobulin infusions, which may induce reversible cerebral vasoconstriction, and may also occur with the use of illicit drugs such as amphetamines, cannabis, cocaine, and lysergic acid diethylamide (LSD). Selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), α-sympathomimetics, nasal decongestants, triptans, ergot alkaloid derivatives, nicotine patches, and herbal medications such as ginseng have also been implicated.

Medication Overuse Headache

Medication overuse headache is one of the most common causes of disabling headache in clinical practice and often goes unrecognized.[1] A paradoxical increase in headache frequency commonly occurs in migraine or cluster headache patients consuming excessive quantities of ergotamine preparations or triptans on a regular basis. Treatment involves gradual withdrawal of the offending drugs and commencement of an alternative prophylactic medication. Chronic analgesic dependency may have a similar effect in chronic tension-vascular headache sufferers, leading to rebound headaches and contributing to the syndrome of chronic daily headache.

Idiopathic Intracranial Hypertension

A number of drugs may cause the idiopathic intracranial hypertension syndrome, characterized by headache, papilledema, diplopia, and visual impairment. These include oral contraceptives, estrogens and progestational agents, growth hormone, anabolic steroids, antibiotics (e.g., tetracyclines, minocycline, ampicillin, nalidixic acid, nitrofurantoin), nonsteroidal anti-inflammatory medications (e.g., naproxen, ibuprofen, indomethacin), vitamin A and retinoids (isotretinoin, etretinate), danazol, amiodarone, thyroxine, ketamine, nitrous oxide, and corticosteroids or corticosteroid withdrawal.

Aseptic Meningitis

Aseptic meningitis may be caused by a variety of drugs including NSAIDs and cotrimoxazole, particularly in patients with systemic connective tissue diseases, and occasionally by other antimicrobials such as sulfasalazine, penicillin, amoxicillin, ciprofloxacin, and cephalosporins; and by carbamazepine and pentoxifylline. Aseptic meningitis may also develop after intravenous immunoglobulin therapy and treatment with other immunomodulatory agents such as infliximab, leflunomide, azathioprine, and monoclonal antibodies such as muromonab-CD3. Intrathecal anesthetics, contrast media, methylprednisolone, methotrexate, and cytarabine may also cause aseptic meningitis.

STROKE

Women taking oral contraceptives have an increased risk of ischemic stroke and cerebral venous thrombosis, but the absolute risk is small in healthy young women without other stroke risk factors who are on low-dose estrogen-progestin preparations. The risk of ischemic stroke is higher in women with migraine and high blood pressure and in smokers and those taking higher-dose contraceptive pills. Oral contraceptives are not thought to increase the risk of hemorrhagic stroke, but have been implicated in subarachnoid hemorrhage, particularly in smokers. The risk of stroke may also be increased by postmenopausal hormone replacement therapy, particularly if commenced more than 5 years after the menopause.[2] Women with breast cancer treated with tamoxifen have an increased risk of ischemic stroke and of other types of stroke including venous sinus thrombosis. There is also a modest increase in the risk of ischemic stroke and myocardial infarction in men on testosterone replacement therapy, particularly in the first 2 years of treatment.[3]

Overmedication with antihypertensive drugs is an important potential cause of iatrogenic ischemic stroke, especially in the elderly and in patients with severe cerebrovascular disease. Patients taking anticoagulants have an increased risk of intracerebral and other forms of intracranial hemorrhage, particularly with long-term or poorly controlled therapy; and there is an increased risk of ischemic stroke in patients with heparin-induced thrombocytopenia. The use of aspirin and other antiplatelet drugs for primary or secondary stroke prevention is also a risk factor for intracerebral hemorrhage.

Intracerebral or subarachnoid hemorrhage may occur following intravenous, oral, or intranasal administration of amphetamines and related compounds that cause acute blood pressure elevation. Recreational use of methamphetamine is an important risk factor for intracerebral hemorrhage and is associated with a fivefold increase in the risk of hemorrhagic stroke, which can occur at an earlier age and has a poorer outcome than in nonusers.[4] Intracranial hemorrhage may also occur in patients taking diet pills, decongestants, and stimulants containing phenylpropanolamine or pseudoephedrine. Intracerebral hemorrhage or ischemic stroke may occur in individuals taking high doses of ephedrine-containing preparations or taking cocaine, amphetamines, methylphenidate, or heroin. These drugs, as well as phenylpropanolamine, pseudoephedrine, oxymetazoline, allopurinol, penicillin, and ergot alkaloids, have also been implicated in causing cerebral vasculitis in some patients.

SEIZURES

Many drugs can induce seizures in healthy individuals, and especially in those with pre-existing epilepsy or a low seizure threshold (Table 32-1). It has been estimated that up to 6 percent of new-onset seizures are drug related and that approximately 10 percent of cases of status epilepticus presenting to an emergency department result from drug toxicity.[5] Some drugs are more likely than others to cause seizures, particularly those that cross the blood–brain barrier and those administered in high doses intravenously or intrathecally. The following classes of drugs have been reported repeatedly to induce seizures, in decreasing order of frequency: antidepressants, stimulants, anticholinergics, and other medications such as baclofen, antihistamines, antipsychotics, naproxen, meperidine, local anesthetics, isoniazid, propoxyphene, methylphenidate, lithium, cyproheptadine, acetylsalicylic acid, and glipizide. With a number of the drugs listed in Table 32-1, seizures have been reported only rarely and the association therefore remains circumstantial.

A number of factors predispose to drug-induced seizures, including a family history of epilepsy and a genetically determined low seizure threshold. Penicillin-induced seizures are more likely to occur with high-dose

TABLE 32-1 ■ Drugs Associated with the Occurrence of Seizures

Antidepressants	Tricyclics, monoamine oxidase inhibitors, SSRIs
Antipsychotics	Phenothiazines, butyrophenones, lithium, clozapine, olanzapine
Analgesics	Fentanyl, alfentanil, morphine, meperidine, pentazocine, propoxyphene, mefenamic acid
Local Anesthetics	Lidocaine, mepivacaine, procaine, bupivacaine
General Anesthetics	Ketamine, halothane, enflurane, methohexital, propofol, isoflurane
Antimicrobials	Penicillins, ampicillin, cephalosporins, imipenem, metronidazole, nalidixic acid, isoniazid, cycloserine, pyrimethamine, acyclovir, ganciclovir, foscarnet
Antineoplastics	Chlorambucil, vincristine, methotrexate, cytarabine, misonidazole, carmustine
Bronchodilators	Aminophylline, theophylline
Sympathomimetics	Ephedrine, terbutaline, phenylpropanolamine
Other Drugs	Antihistamines, anticholinergics, anticonvulsants, chloroquine, baclofen, cyclosporine, azathioprine, β-adrenergic blockers, flumazenil, disopyramide, bromocriptine, domperidone, phencyclidine, amphetamines, methylphenidate, famotidine, isotretinoin, ondansetron, allopurinol, oxytocin, erythropoietin

intravenous or intrathecal administration, and in patients with impaired renal failure who have high blood levels of the drug. Other drugs that may cause seizures when they accumulate as a result of reduced renal excretion include meperidine, imipenem, nalidixic acid, cephalosporins, cimetidine, lithium, and erythropoietin. Seizures have also been reported in patients treated with cyclosporine, especially in renal or liver transplant patients who have high blood levels of the drug.

A number of therapeutic agents such as oxytocin, carbamazepine, and the SSRIs can cause seizures by inducing hyponatremia. Withdrawal of benzodiazepines, barbiturates, tricyclic antidepressants, alcohol, or baclofen is another important cause of seizures, particularly if the withdrawal is too abrupt. Withdrawal of anticonvulsant drugs in epileptic patients is also an important cause of seizures or even status epilepticus, and should always be gradual.

Conversely, excessively high doses and serum concentrations of certain anticonvulsants may aggravate epilepsy or induce new seizure types or even status epilepticus. Carbamazepine may aggravate absences and myoclonic or atonic seizures. Benzodiazepines may induce tonic seizures and status epilepticus in patients with the Lennox–Gastaut syndrome. Valproic acid and vigabatrin may occasionally induce status epilepticus. Gabapentin may have an adverse effect on myoclonic epilepsy, as may topiramate on focal epilepsy, and tiagabine may induce nonconvulsive status epilepticus.

The convulsant effects of certain drugs, such as isoniazid, aminophylline, local anesthetics, phencyclidine, and meperidine, are dose related, but other drugs may cause seizures even with therapeutic doses and blood levels. These include theophylline, tricyclic antidepressants, and phenothiazines. The aliphatic phenothiazines chlorpromazine, promazine, and prochlorperazine are more likely to induce seizures than the piperazine group, such as fluphenazine and trifluoperazine. Seizures have also been reported with the atypical neuroleptics clozapine, olanzapine, risperidone, and sertindole. Most classes of antidepressant may induce seizures, including SSRIs, SNRIs, tricyclics, bupropion, mirtazapine, reboxetine, and trazodone, although the risk is low. Lithium-induced seizures are well known and generally occur when plasma levels exceed 3.0 mEq/L.

ENCEPHALOPATHY

Certain drugs such as lithium and acyclovir may cause a diffuse disturbance of cerebral function leading to tremor, asterixis, myoclonus, seizures, ataxia, confusion, and obtundation. Such a syndrome may be caused by lithium toxicity, but it sometimes occurs even when blood levels of the drug are within the recommended therapeutic range.

A severe diffuse encephalopathy with associated focal neurologic features has recently been recognized in patients with various forms of malignancy undergoing chimeric antigen receptor T-cell therapy.[6]

High doses of penicillin and cephalosporins may also cause an acute encephalopathy, particularly in patients with impaired renal function, as may a variety of other drugs including lidocaine, tocainide, benzodiazepines, vigabatrin, valproic acid, phenytoin, carbamazepine, baclofen, isoniazid, levodopa, mefloquine, sulfonamides, podophyllin, L-asparaginase, thymidine, 5-fluorouracil, carmustine (BCNU), mechlorethamine, *N*-phosphonacetyl-L-aspartic acid (PALA), cytarabine, fludarabine, doxorubicin, and intrathecal metrizamide. In the past, a myoclonic encephalopathy was recognized in patients with prolonged exposure to bismuth-containing preparations or with aluminum toxicity in those undergoing hemodialysis ("dialysis encephalopathy"), and with carisoprodol overdosage.

A progressive leukoencephalopathy characterized by dementia, dysarthria, ataxia, and paralysis, at times followed by seizures, coma, and death, may occur in patients treated with high-dose intrathecal, intraventricular, or intravenous methotrexate, particularly after cranial or craniospinal radiotherapy. A posterior leukoencephalopathy with headache, seizures, cortical blindness, and parieto-occipital lesions has been increasingly recognized in patients treated with cyclosporine (Fig. 32-1). The condition is often associated with hypertension and high blood drug levels and is usually reversible. Other drugs that have been associated with the development of a leukoencephalopathy include capecitabine, cisplatin, cytarabine, 5-fluorouracil, fludarabine, ifosfamide, amphotericin B, interferons, interleukin-2, levamisole, tacrolimus, melarsoprol, and bevacizumab, as well as heroin, synthetic cannabinoids, and other drugs of addiction.

There is increasing awareness of the higher risk of developing the JC virus–associated disorder progressive multifocal leukoencephalopathy (PML) in individuals treated with immunomodulatory biologics such as natalizumab (anti-α4-integrin) and rituximab (anti-CD20).

DRUG-INDUCED COMA

Drugs are a common and important cause of coma resulting from accidental or self-administered overdosage. The drugs can be classified into those that have a direct

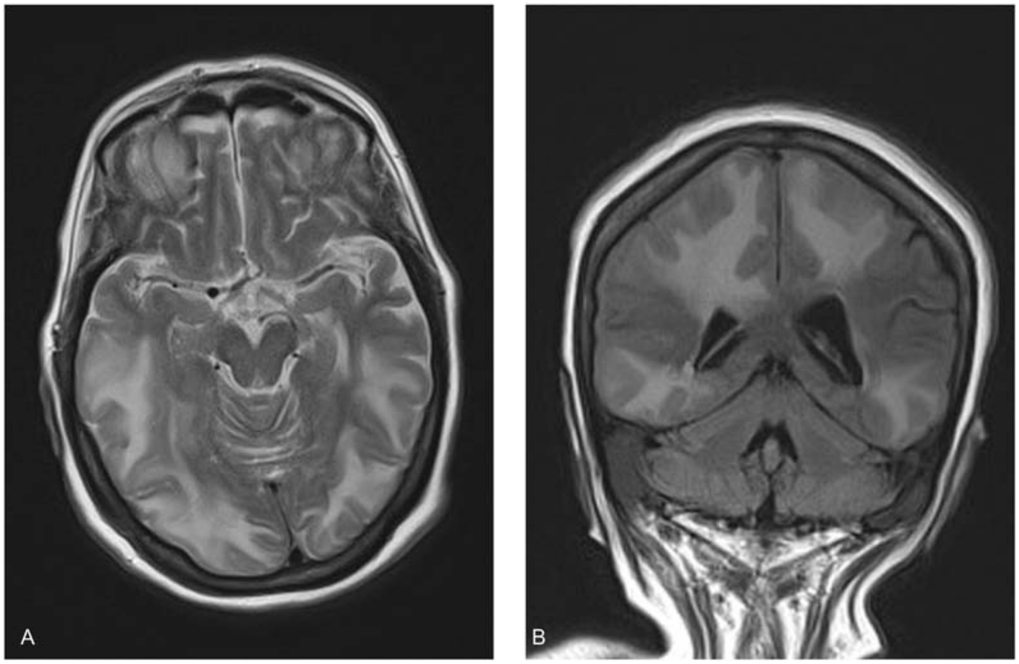

FIGURE 32-1 ■ Axial (*A*) and coronal (*B*) T2-weighted MRI of the brain showing findings of posterior reversible encephalopathy syndrome in a patient with mixed connective tissue disease receiving cyclosporine.

depressant effect on the brain such as hypnotics, sedatives, antidepressants, analgesics, or various drug combinations, and those that cause coma through indirect effects, such as insulin, antihypertensives, and antiarrhythmics. Other drugs that may cause depression of consciousness include phenothiazines, salicylates, acetaminophen (which can cause severe hepatic damage), paraldehyde, acyclovir, and valproic acid.

Certain neurologic findings are characteristic of drug-induced coma. The pupils are typically small and reactive, but may be dilated and fixed in severe barbiturate intoxication or pinpoint in opiate poisoning. The corneal reflexes are preserved but may be lost in profound drug-induced coma. Both spontaneous and reflex eye movements are depressed early, particularly with barbiturate, tricyclic, and phenytoin intoxication, with the eyes being fixed and divergent, without spontaneous roving eye movements, and with impaired or absent oculocephalic and oculovestibular reflexes. Muscle tone is often reduced and the tendon reflexes are depressed, with flexor plantar responses, but there may be hypertonia, hyperreflexia, decerebrate posturing, and extensor plantar responses, particularly if there has been superadded cerebral hypoxia. Muscle twitching, choreoathetosis, myoclonus, and seizures may all occur in coma caused by tricyclic agents or lithium toxicity.

The electroencephalogram (EEG) can sometimes provide a clue to identifying the causative drug. In drug-induced coma it usually shows diffuse slowing, but with barbiturate or benzodiazepine intoxication there is typically a predominance of beta activity ("beta coma"). Alpha-pattern coma, or mixed alpha and beta rhythms, may also occur with benzodiazepine or with chlormethiazole intoxication.

NEUROPSYCHIATRIC DISORDERS

Psychiatric adverse drug reactions are common in clinical practice and may take various forms.

Behavioral Toxicity

A variety of nonspecific symptoms including drowsiness, insomnia, irritability, restlessness, anxiety, mood changes, vivid dreams and nightmares, and increased sensitivity to light and sound may occur with a wide range of medications and may be the prelude to a more florid delirious state, but usually subside with withdrawal of the drug or dose reduction. Such symptoms are encountered most frequently with tricyclic agents, lithium, amphetamines, phenothiazines, barbiturates, glucocorticoids, cholinergic drugs, levodopa, antihistamines, and acetylcholinesterase inhibitors, as well as some anticonvulsants. Similar symptoms may also occur following withdrawal of certain medications such as benzodiazepines and SSRIs.

Delirium and Confusional States

Drugs are an important cause of delirium and confusional states, particularly in the elderly. Various drugs may cause such reactions, including sedatives, tranquilizers, hypnotics, narcotics, antihistamines, and anticholinergics. Other important causes include antiparkinsonian drugs and antidepressants, in particular the SSRIs and SNRIs, which have been associated with the serotonin syndrome (discussed later), as well as interactions between serotonergic drugs and monoamine oxidase inhibitors or tricyclic agents and other drugs. Abrupt withdrawal of SSRI drugs may also precipitate a confusional or delirious state with associated twitching, hypertonia, and sensory symptoms. Less frequent causes of drug-induced delirium include cephalosporin and macrolide and fluoroquinolone antibiotics. Delirious states with associated motor hyperactivity have also been reported frequently with the influenza antiviral agent oseltamivir.

Mood Disorders

Drug-induced depressive reactions are common. Reserpine and α-methyldopa were among the first drugs recognized to cause depression, but depression is uncommon with the newer generations of antihypertensive agents. Mood disturbance with manic features is the most common psychiatric side effect of corticosteroids, and depression is the most common psychiatric symptom in patients taking levodopa. Depression may also occur in patients on a variety of other medications, including oral contraceptives, anabolic steroids, tetrabenazine, digoxin, indomethacin, naproxen, disulfiram, sulfonamides, cycloserine, retinoids, antineoplastics, antiepileptics, baclofen, barbiturates, benzodiazepines, phenothiazines, butyrophenones, and interferons. It may also follow benzodiazepine, amphetamine, or fenfluramine withdrawal.

Although euphoria is a common drug-induced side effect, manic or hypomanic reactions are uncommon. Such reactions may however occur with a variety of drugs including glucocorticoids, corticotropin, anabolic steroids, thyroxine, captopril, chloroquine, isoniazid, ranitidine and cimetidine, dopaminergic agents, baclofen, opiates, pentazocine, monoamine oxidase inhibitors, tricyclic agents, iproniazid, cyclosporine, sympathomimetic amines, amphetamines, benzodiazepines, procyclidine, phenylpropanolamine, and hallucinogens. Antidepressants may also induce mania, especially in individuals with bipolar disorder. Increased risk of a manic episode has been reported with tricyclic antidepressants and monoamine oxidase inhibitors, but not with standard doses of SSRIs.

Psychoses

Various drugs have been reported to cause paranoid or schizophreniform psychotic reactions characterized by delusions, hallucinations, and emotional and thought disorder, particularly in the elderly. Although these drug-induced disorders closely resemble the naturally occurring psychoses, such individuals do not appear predisposed to develop a psychotic disorder subsequently.

Hallucinatory States

Various drugs can cause hallucinations without other features of delirium or psychosis. The hallucinations usually tend to be visual, extremely vivid and colored, and often of animals, sometimes having microptic or Lilliputian dimensions. The most common causative drugs are tricyclic agents, benzodiazepines, vigabatrin, bromides, methylphenidate, atropine and other anticholinergic drugs after parenteral or even topical administration into the eye, ephedrine, amantadine, bromocriptine, pergolide, levodopa, digoxin, diltiazem, prazosin, captopril, disopyramide, pentazocine, buprenorphine, indomethacin, salicylates, cimetidine, aminophylline, acyclovir, and cyproheptadine, as well as cannabis and LSD. Auditory and less often visual hallucinations are also a feature of withdrawal from alcohol, barbiturates, benzodiazepines, and baclofen.

Cognitive Impairment

Various drugs may cause transient memory impairment, including baclofen, pregabalin, benzhexol, isoniazid, propranolol, antidepressants (SSRIs and tricyclics), and statins. More severe, but reversible, cognitive impairment, which may mimic dementia, can also develop with chronic intake of benzodiazepines, barbiturates, bromides, and chlorpromazine, with anticonvulsant overdosage, and with glucocorticoid and interleukin administration. These medications may also aggravate cognitive functions in patients who already have mild cognitive impairment and should therefore be administered with caution.

A number of antiepileptic drugs may adversely affect cognitive functions. Early studies suggested that such effects were less frequent with carbamazepine or sodium valproate than with phenytoin or phenobarbital. However, more recent studies have shown that, at therapeutic serum concentrations, the adverse effects are comparable for these drugs. The newer antiepileptics gabapentin, lamotrigine, vigabatrin, tiagabine, remacemide, topiramate, and levetiracetam have fewer cognitive effects.

Several lines of evidence, including pretrial safety and tolerability testing, postmarketing surveillance, and multiple case reports have linked statins to short-term reversible cognitive impairment, particularly in relation to short-term memory. However, this was not confirmed in a systematic review and meta-analysis of randomized controlled trials.[7] In spite of this, it does appear that memory impairment can occur in a small proportion of people taking statins and that the risk may be greater in individuals on the more potent lipophilic statins, atorvastatin and simvastatin. Further prospective studies are required to determine whether certain subpopulations of statin users are at greater risk and to identify other patient-specific factors that may allow such individuals to be identified.[7]

MOVEMENT DISORDERS

Several drugs, in particular dopamine-receptor blocking antipsychotics and antiemetics, may induce involuntary movements or abnormalities of movement, posture, or gait that may resemble naturally occurring extrapyramidal disorders.[8] These same drugs may also aggravate pre-existing extrapyramidal disorders such as Parkinson disease and should therefore be used with caution in such patients. There is marked individual variability in the susceptibility to these reactions, some patients developing side effects even with small doses of a drug, whereas others on much higher doses are unaffected. Sex, age, and genetic factors may all play a part in determining individual susceptibility.

Akathisia

Akathisia is a state of motor restlessness characterized by an uncontrollable urge to move about, pace, or even run incessantly. The condition typically occurs in patients taking dopamine-blocking agents such as phenothiazine derivatives and less frequently with butyrophenones, benzodiazepines, tricyclic agents, SSRIs, levodopa, lithium, monoamine oxidase inhibitors, and vigabatrin. The reported incidence of akathisia with antipsychotic drugs ranges from 20 to 75 percent and is less frequent with the atypical antipsychotics. It usually remits within days or weeks of withdrawal of the neuroleptic drug, but may persist for several months and is occasionally permanent.

The most effective treatment for akathisia is to withdraw or lower the dose of the causative drug. Benztropine or diphenhydramine is usually effective in controlling akathisia when given intramuscularly or intravenously, and propranolol, clonazepam, and amantadine may also be beneficial.

Acute Dystonic-Dyskinetic Reactions

Acute dystonic reactions are a well-recognized side effect of antipsychotic or antiemetic drugs, in particular the phenothiazines (fluphenazine, prochlorperazine) and butyrophenones (haloperidol), metoclopamide, and, less frequently, promethazine, tricyclic antidepressants and SSRIs, phenytoin, carbamazepine, propranolol, ondansetron, flunarizine, and cinnarizine. The onset is usually within the first few days of starting treatment, but can be almost immediate, and may be quite abrupt. The dystonia may be confined to the head and neck, causing facial grimacing, jaw spasms and trismus, abnormal tongue movements, blepharospasm, oculogyric crises, orofacial dyskinesias, and torticollis or retrocollis. In some cases the dystonia is more generalized, with slow writhing movements or prolonged tonic spasms of the limb and axial muscles resulting in carpopedal spasm, opisthotonos, lordosis, tortipelvis, and a bizarre gait. Rarely laryngospasm may occur. Because of their bizarre and protean nature, the movements can be mistaken for hysteria. The differential diagnosis also includes hyperventilation, tetany, tetanus, strychnine poisoning, and epilepsy. Despite their dramatic and at times alarming nature, the acute dystonic reactions are self-limiting and will usually remit once the drug is withdrawn. Severe reactions can be terminated by intravenous or intramuscular benztropine or promethazine, or intravenous diazepam.

Tardive Dyskinesia and Other Tardive Syndromes

Tardive dyskinesia and other tardive syndromes may occur in patients treated with a variety of dopamine antagonists.[8] They are most commonly seen in patients with schizophrenia or schizoaffective or bipolar disorder treated with antipsychotic medications for long periods, but may also occur with prolonged administration of metoclopramide, chlorpromazine, thioridazine, promethazine, prochlorperazine, amoxapine, perphenazine, trifluoperazine, flunarizine, cinnarizine, and antidepressants. Early studies found tardive dyskinesia in up to 50 percent of patients treated with the older antipsychotic drugs, but the frequency has declined since the introduction of the second- and third-generation antipsychotics. Tardive dyskinesia usually develops after more than 12 months of continuous therapy, although it has been reported with periods as short as 3 months. It may present after cessation of therapy. The condition is more common and is often more severe in the elderly, in whom it is less likely to remit.

The dyskinesia typically takes the form of an orobuccal dyskinesia with lip smacking and pursing; sucking; jaw opening and closing; protruding, side-to-side, or writhing movements of the tongue; and facial grimacing. The movements tend to be stereotyped and may interfere with speaking and swallowing. In some cases more generalized choreoathetotic movements of the limbs and trunk and repetitive foot-tapping movements are present, at times resembling Huntington chorea. Less frequently, dystonic posturing of the neck and myoclonic jerking of the distal extremities are present as well. Akathisia or parkinsonism may also occur.

Tardive dystonia is less common and tends to occur in younger individuals, particularly men. It is distinguished from tardive dyskinesia by the more sustained abnormal movements and postures, which may be focal or more generalized and may involve the jaw, neck, limbs, or trunk. Tardive dystonia is often more disabling than tardive dyskinesia. Other tardive syndromes include akathisia, chorea, myoclonus, tremor, tics, and oculogyric crises.

The severity of tardive dyskinesia is variable and it may remit in up to 40 percent of cases, even on continued therapy. Occasionally remission may occur even several years after withdrawal of antipsychotic medications. Interruption of therapy when dyskinesia first develops may be beneficial, but there is some evidence that repeated interruptions may actually increase the risk of persistence.

The treatment of tardive dyskinesia is problematic.[8] Many medications have been used in the past, including dopaminergic agents (tetrabenazine, bromocriptine, and levodopa) and drugs with a cholinergic action, such as choline and deanol. Other drugs reported to be beneficial include amantadine, clonazepam, baclofen, propranolol, diazepam, tocopherol, *Ginkgo biloba*, levetiracetam, and calcium-channel blockers. None has been consistently effective. More recently, the VMAT2 inhibitors deutetrabenazine and valbenazine have become established as evidence-based therapies for tardive syndromes.[8]

In cases of focal or segmental tardive dystonia or orobuccal dyskinesia, botulinum toxin injections may be effective. Deep brain stimulation may need to be considered in medically refractory cases.

Levodopa-Induced Dyskinesias

Choreoathetotic dyskinetic reactions involving the face, tongue, limbs, and trunk are common in patients with Parkinson disease treated with levodopa and other dopaminergic agents, developing in about 50 percent of patients after 4 to 5 years of treatment, usually starting on the side of the body that is more affected by the disease. Levodopa-induced dyskinesias are thought to be due to nonphysiologic phasic stimulation of dopamine receptors in the striatum and are dose-dependent.[9] In some patients they develop early during treatment with levodopa or dopamine agonists and usually respond to a reduction in drug dose. With prolonged treatment, dyskinesias become an increasing problem, tending to occur at times of peak response to levodopa (peak-dose dyskinesia) but sometimes occurring as blood levels decline (biphasic dyskinesia) and alternating with periods of akinesia and severe rigidity (the so-called on–off phenomenon). The administration of smaller, more frequent doses of levodopa, or a reduction in overall dose and the introduction of a dopamine agonist is often helpful in alleviating this common complication of prolonged levodopa therapy. Other medications that can be beneficial include amantadine and leviracetam, and a number of novel pharmacologic approaches are under development.[9] However, severe and disabling dyskinesias are usually an indication for deep brain stimulation.

Chorea and Choreoathetosis

A number of drugs may cause chorea, which is characterized by multifocal, nonstereotyped, "fidgety" or jerky movements and may co-exist with the slower movements of athetosis or with dystonia. Chorea or choreoathetosis has been reported with many drugs

including anticonvulsants in high doses (e.g., phenytoin, ethosuximide, valproic acid, carbamazepine, phenobarbital), clonazepam withdrawal, anticholinergic drugs (e.g., high doses of benzhexol), tricyclic agents, fluoxetine, amphetamines, methylphenidate, amoxapine, pemoline, cimetidine, theophylline, aminophylline, lithium, methadone, antihistamines, cyclosporine, oxymetholone, intrathecal baclofen, and certain oral contraceptives. Chorea has also been well described with cocaine use ("crack dancing").

Tics

A condition resembling Gilles de la Tourette syndrome has been reported in children after the administration of dextroamphetamine, methylphenidate, or pemoline. Other antipsychotic drugs as well as opiates, clonazepam, carbamazepine, phenobarbital, and fluoxetine have also been reported to cause tics.

Myoclonus

Drug-induced myoclonus may occur particularly in patients treated with antipsychotic and tricyclic antidepressant drugs or lithium carbonate and has also been reported with a variety of other drugs including propofol, clozapine, vigabatrin, phenytoin, fluvoxamine, chlorambucil, opioids, antibiotics (e.g., penicillin, ticarcillin, carbenicillin, imipenem, cephalosporins), and calcium-channel blockers. Reversible multifocal myoclonus may also occur with gabapentin or pregabalin treatment, particularly in patients with renal insufficiency. A clinical picture resembling Creutzfeldt–Jakob disease with myoclonus, tremor, cerebellar and extrapyramidal manifestations, cognitive impairment, and periodic sharp-wave EEG complexes has been reported in patients with lithium toxicity.

Tremor

Many drugs may cause or aggravate tremor. These include β_2-adrenergic agonists (e.g., salbutamol, salmeterol); sympathomimetic drugs (e.g., ephedrine, pseudoephedrine, phenylpropanolamine); antiseizure agents (e.g., sodium valproate); antidepressants and mood stabilizers (e.g., tricyclic drugs, SSRIs, lithium); neuroleptic agents (e.g., phenothiazines, butyrophenones); antiarrhythmics (amiodarone, procainamide, mexiletine); chemotherapeutic agents (e.g., doxorubicin, cytarabine, thalidomide); and some immunosuppressants (e.g., cyclosporine, tacrolimus), as well as thyroxine, glucocorticoids, hypoglycemic agents, levodopa, amphetamines, theophylline, and aminophylline.

A postural tremor of the hands, head, and trunk resembling essential tremor is not uncommon in patients treated with sodium valproate. This usually develops over a period of several months and remits when the drug is stopped or the dose is reduced. Treatment with propranolol or amantadine may alleviate the tremor. Postural or action tremor is also an early manifestation of lithium intoxication and is common even with therapeutic doses. A postural tremor has been reported in up to 40 percent of patients on cyclosporine.

A "flapping" tremor (asterixis) may occur in patients treated with various drugs including phenytoin, phenobarbital, carbamazepine, sodium valproate, methyldopa, ceftazidime, lithium, and tocainide.

Parkinsonism

Drug-induced parkinsonism is probably the most common drug-induced movement disorder. It can occur at any age, but is more common in the elderly. Although it may closely resemble idiopathic Parkinson disease, early differentiation is important in view of the markedly different prognosis in the two conditions.[8,10] Bradykinesis is usually the most prominent clinical feature, with associated facial masking, rigidity, tremor, and altered gait. Unlike idiopathic Parkinson disease, the symptoms are usually, but not always, bilateral from the outset, and the incidence of tremor is lower.

The drugs most commonly implicated are neuroleptics and antipsychotic medications with central dopamine-blocking actions, including phenothiazines (e.g., chlorpromazine, fluphenazine, cyamemazine), butyrophenones (e.g., haloperidol, droperidol), benzamides (e.g., sulpiride, amisulpride, tiapride), and other atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, quetiapine). Other drugs that have been implicated include antidepressants (SSRIs and tricyclics); calcium-channel blockers (flunarizine, cinnarizine); antiemetics (metoclopramide, prochlorperazine); and anticonvulsants (valproic acid, phenytoin) (Table 32-2). These drugs may also aggravate the symptoms of early idiopathic Parkinson disease or lead to the development of signs in the premotor or prodromal stages of the disease.

Drug-induced parkinsonism is usually reversible, with most patients improving gradually following drug

TABLE 32-2 ■ Major Causes of Drug-Induced Parkinsonism[8,10]

Antipsychotics (typical)	Haloperidol, droperidol, chlorpromazine, fluphenazine, cyamemazine, loxapine, pimozide, flupenthixol, zuclopenthixol
Antipsychotics (atypical)	Amisulpride, sulpiride, tiapride, clozapine, olanzapine, quetiapine, risperidone, aripiprazole, ziprapisone
Antidepressants	Citalopram, paroxetine, fluoxetine, fluvoxamine, escitalopram, sertraline, venlafaxine, mirtazapine, amitriptyline, clomipramine, phenelzine
Calcium-Channel Blockers	Flunarizine, cinnarizine, verapamil, diltiazem
Antiemetics	Prochlorperazine, metoclopramide, domperidone
Miscellaneous	Lithium, tetrabenazine, valproic acid, donepezil, pyridostigmine, amiodarone, captopril, cyclosporine, tacrolimus, rifampicin, acyclovir, vincristine, trimetazidine, H_1-antihistamines, meprobamate, reserpine

withdrawal or dose reduction. In some cases, spontaneous improvement occurs even if the causative medication is continued. However, tremor may persist after drug withdrawal and sometimes there is continued deterioration in motor signs, suggesting that the medication may have unmasked the symptoms of idiopathic Parkinson disease. Administration of an anticholinergic agent, such as benzhexol or benztropine, may reduce or reverse the parkinsonian symptoms, but dopaminergic medication may be required in some cases. In patients who need to continue on neuroleptic therapy, switching to a lower risk medication such as quetiapine or clozapine is usually recommended.

CEREBELLAR SYNDROMES

Various drugs may cause ataxia, incoordination, and other manifestations of cerebellar dysfunction. These drugs include sedatives and tranquilizers such as barbiturates, benzodiazepines, chloral hydrate, and paraldehyde, as well as anticonvulsants such as phenytoin, carbamazepine, and primidone whose effects are usually dose dependent. Individual tolerance to these drugs varies considerably, but in general symptoms are more likely to develop with higher doses, and if dose escalation is too rapid, although with pregabalin and gabapentin symptoms may develop even at relatively low doses. Signs of cerebellar dysfunction are caused more rarely by phenothiazines, monoamine oxidase inhibitors, reserpine, thioxanthenes, and lithium. Lithium may cause an isolated cerebellar ataxia or more diffuse encephalopathy, even with blood levels within the therapeutic range. A cerebellar syndrome has also been reported in bone marrow and liver transplant recipients treated with cyclosporine; in patients with leukemia or lymphoma on high doses of cytarabine; in cancer patients treated with high- or low-dose fluorouracil; and in patients with impaired renal function taking nitrofurantoin or perhexiline.

These disorders are usually reversible when the causative agent is withdrawn or the dose is adjusted, but there are reports of permanent cerebellar dysfunction and cerebellar atrophy in some patients treated with lithium or phenytoin.

NEUROLEPTIC MALIGNANT SYNDROME

The neuroleptic malignant syndrome is a serious and potentially lethal complication of treatment with antipsychotic and antiemetic medications that reduce dopaminergic transmission. It is characterized clinically by hyperpyrexia, severe generalized muscular rigidity, and an elevated serum creatine kinase (CK) level (which are considered major diagnostic criteria); tachycardia, abnormal blood pressure, tachypnea (autonomic manifestations); and altered consciousness, diaphoresis, and leukocytosis (which are the minor diagnostic criteria). Three major criteria, or two major and four minor criteria are considered very suggestive of the diagnosis in the right clinical context. Other less frequent motor abnormalities include tremor, myoclonus, dystonia, opisthotonos, trismus, and chorea.

The drugs most frequently implicated are haloperidol, fluphenazine and other phenothiazines, thioxanthenes, or combinations of these drugs with each other or with lithium, metoclopramide, loxapine, or tricyclic agents. Clozapine and olanzapine have also been implicated. Risk factors include high drug doses, rapid dose increases, parenteral administration, and switching from one potentially causative drug to another. The condition may occur with both high and low doses of either high- or low-potency neuroleptics and may develop after neuroleptic therapy is begun, after an increase in dose, or after the introduction of a second more potent drug. The current view is that neuroleptic malignant syndrome is due to profound dopamine receptor blockade in the striatum and in thermoregulatory and vasomotor centers in the hypothalamus.

In mild cases, complete recovery may occur within days or weeks of stopping the causative drug, but in severe cases rhabdomyolysis, myoglobinuria, metabolic acidosis, renal failure, coagulation defects, respiratory failure, shock, seizures, and coma may develop and there is a mortality rate of approximately 6 percent even in the modern era.[11] Treatment involves discontinuation of the causative drug together with rapid cooling, control of agitation with parenteral benzodiazepines, restoration of fluid and electrolyte balance, and management of any other complications. Specific medications that are beneficial in reversing rigidity and hyperthermia and hastening recovery include dantrolene, bromocriptine, amantadine, levodopa, or a combination of these drugs.

A disorder resembling neuroleptic malignant syndrome may also occur after abrupt levodopa or dopamine agonist withdrawal in patients with Parkinson disease, and after withdrawal of intrathecal baclofen.

SEROTONIN SYNDROME

The serotonin syndrome is a closely related disorder that sometimes is difficult to distinguish from neuroleptic malignant syndrome and which can also be life-threatening in severe cases. It can occur after initiation, increase in dose, or overdose of one of the SSRI or SNRI antidepressants, or with combination therapy. Other drugs that have been implicated less frequently include other classes of antidepressants such as tricyclics, monoamine oxidase inhibitors, and bupropion; opioids, triptans, lithium, antinausea medications, and dextromethorphan-containing cough suppressants; as well as some herbal supplements (e.g., St John's wort and ginseng) and recreational drugs (e.g., LSD, ecstasy, cocaine, and amphetamines).

The features of the serotonin syndrome include high fever, tachycardia, labile blood pressure and autonomic instability, confusion, agitation, tremor, myoclonus, shivering, seizures, piloerection, hyperreflexia, and incoordination. Muscular rigidity and hyperthermia tend to be less severe than in the neuroleptic malignant syndrome; some of the other typical features, such as prodromal nausea, vomiting, and diarrhea, and shivering, hyperreflexia, myoclonus, and ataxia are uncommon in neuroleptic malignant syndrome.

Cessation of the causative drug is critical if the diagnosis is suspected. Although mild cases may recover rapidly within a few days, patients with suspected serotonin syndrome should be hospitalized for observation and treatment. Key aspects of management include maintenance of hydration with intravenous fluids, sedation and control of seizures with benzodiazepines, and administration of cyproheptadine to block serotonin production.

OTOTOXICITY

More than 150 drugs are known to have ototoxic effects, causing cochlear or vestibular damage to the inner ear.[12] Tinnitus is usually the first symptom of cochleotoxicity and, when persistent, is the forerunner of impending hearing loss. Vestibulotoxicity results in vertigo, oscillopsia, and balance impairment, particularly in subdued light.

The most important ototoxic drugs are the aminoglycoside antibiotics, which may cause irreversible inner ear damage after parenteral, oral, or even topical administration. Since these agents are excreted through the kidneys, ototoxicity is more likely to develop in individuals with renal insufficiency. All the aminoglycosides can cause cochlear or vestibular toxicity. Some (e.g., neomycin, kanamycin, amikacin, and vancomycin) are principally cochleotoxic, whereas others (e.g., gentamicin and streptomycin) are preferentially vestibulotoxic, and tobramycin is both vestibulotoxic and cochleotoxic.

Vertical oscillation of the surroundings on movement ("bobbing oscillopsia") is highly characteristic of the vestibulopathy caused by the aminoglycoside antibiotics. Hearing loss affects the high frequencies initially and is usually irreversible. It may develop within a few days of commencing treatment, but more often is delayed and may even develop after the drug is stopped. As a group, the aminoglycosides cause degeneration of the sensory hair cells of the cochlea, the outer hair cells being most severely affected, accounting for the preferential loss of higher frequencies, whereas gentamycin selectively destroys the vestibular hair cells. It is essential to have a high level of awareness of this serious complication, to monitor blood levels of the drug, to avoid prolonged courses of gentamycin, and to discontinue the drug if early symptoms of vestibulotoxicity develop. However, some patients may still develop irreversible vestibulotoxicity even when blood levels are maintained within the recommended range, and the onset of symptoms may be delayed.

Other ototoxic antibiotics include minocycline (which is almost exclusively vestibulotoxic), colistin, polymyxin

B, erythromycin (which may cause reversible deafness after oral or intravenous administration), metronidazole, vancomycin, and rarely, procaine penicillin, cephalexin, and chloramphenicol.

The loop diuretics furosemide, ethacrynic acid, and bumetanide are also ototoxic, especially in patients with renal or hepatic impairment or those also taking an aminoglycoside antibiotic. Salicylates, in particular aspirin, may cause tinnitus, deafness, and vertigo when the serum concentration approaches 300 mg/L. Quinine may cause tinnitus and reversible low-tone hearing loss in a small proportion of patients taking the drug and an idiosyncratic mechanism seems to be involved. Prolonged high-dose administration of chloroquine may cause irreversible tinnitus and perceptive deafness. A number of cytotoxic drugs including cisplatin, vincristine, misonidazole, bleomycin, and mustine hydrochloride may cause hearing loss. Cisplatin causes a high incidence of tinnitus and high-tone hearing loss; recording of brainstem auditory evoked potentials is helpful in detecting early involvement of the auditory pathway.

Other ototoxic drugs include quinidine, deferoxamine, and sildenafil. Practolol caused combined sensorineural deafness and conductive hearing loss due to serous otitis media when it was in use. There are also rare reports of hearing loss or vestibular dysfunction in patients taking propoxyphene, naproxen, indomethacin, sulindac, metoprolol, nortriptyline, propylthiouracil, flecainide, and both interferon-alpha and beta.

VISUAL DISORDERS

Drug-induced visual disorders may result from effects on the pupil, refractive mechanisms, retina, optic nerve, and central visual pathways.

Pupillary Changes

Parasympathomimetic drugs such as carbachol and neostigmine cause miosis, as may morphine, chloral hydrate, and phenothiazines. Mydriasis is more often drug-induced and potentially more serious as it may precipitate acute angle-closure glaucoma in susceptible individuals. Drugs that may cause mydriasis and cycloplegia with blurring of near vision include anticholinergics, antihistamines, monoamine oxidase inhibitors, tricyclic antidepressants, chlorpropamide, indomethacin, hexamethonium, fenfluramine, oral contraceptives, amphetamines, and LSD.

Refractive Changes

In addition to the drugs mentioned earlier that may cause cycloplegia and induced hypermetropia, certain drugs cause a transient myopia as a result of fluid shifts between the lens and the aqueous humor. These include oral diuretics (chlorothiazide, hydrochlorothiazide, chlorthalidone, and acetazolamide), tetracyclines, sulfonamides, corticosteroids and corticotropin, stilbestrol, phenytoin, thiamine, bromocriptine, and arsenicals, as well as insulin and oral hypoglycemic agents.

Retinopathy

Chloroquine, hydroxychloroquine, mepacrine, and amodiaquine may cause a pigmentary maculopathy and retinopathy with central and peripheral field defects and impairment of central vision after prolonged administration. Patients on these drugs should have regular neuro-ophthalmic examinations, electroretinography, and electro-oculography to detect early signs of retinopathy. Phenothiazines in high doses may produce a progressive choroidoretinopathy; cardiac glycosides, methylphenidate, and cephaloridine have also been reported to cause pigmentary retinopathy. Macular edema has been reported with fingolimod, a new oral therapeutic agent for multiple sclerosis, and normally resolves on cessation of treatment. It may rarely also be caused by chlorothiazide, acetazolamide, and oral contraceptives.

Other drugs that may interfere with vision through retinal effects include indomethacin, quinine, tamoxifen, ethambutol, diethylcarbamazine, and vigabatrin, which has been found to cause symptomatic, or more often asymptomatic, visual field constriction.

Optic Neuropathy

A number of antimicrobial agents including linezolid, chloramphenicol, isoniazid, paraminosalicylate, streptomycin, ethambutol, sulfonamides, griseofulvin, and dapsone can cause a toxic optic neuropathy. Other drugs implicated in causing optic neuropathy include amiodarone, chlorpropamide, chlorambucil, cisplatin, 5-fluorouracil, vincristine, interferon-alpha, penicillamine, disulfiram, nonsteroidal anti-inflammatories, monoamine oxidase inhibitors, morphine, retinoids, organic arsenicals, cardiac glycosides, dideoxyinosine, omeprazole.

Certain drugs, such as sildenafil (Viagra) and tadalafil (Cialis) used for erectile dysfunction, and ergotamine may all precipitate an acute ischemic optic neuropathy, particularly in individuals with a high arteriosclerotic risk profile.

There have also been case reports of the tissue necrosis factor alpha (TNF-α) inhibitors infliximab, adalimumab, and etanercept causing optic neuritis, with enhancement of the optic nerve on MRI in some cases; some patients have associated cerebral demyelinating lesions.

In the past, optic neuropathy and optic atrophy were also part of the subacute myelo-opticoneuropathy (SMON) syndrome associated with the antifungal/antiprotozoal drug clioquinol, when it was used for the treatment of enteric infections.

Disorders of Color Vision

Disturbances of color vision may result from the effects of various drugs on retinal cone receptors or from optic nerve dysfunction. Xanthopsia (yellow vision) may occur with sulfonamides, streptomycin, methaqualone, barbiturates, digitalis derivatives, thiazide diuretics, and the anthelmintic drug santonin. Sildenafil (Viagra) and tadalafin (Cialis) can cause blue vision, which is reversible. Other drugs that may cause altered color vision include nalidixic acid, oral contraceptives, cannabis, LSD, and the older anticonvulsants troxidone and paramethadione.

Cortical Blindness

Cortical blindness may rarely occur after episodes of severe hypotension during anesthesia or after treatment of hypertension. It has also been reported as a complication of chemotherapy during childhood and of excessive doses of salicylates or barbiturates. It may also occur as part of a posterior reversible encephalopathy syndrome in patients treated with cyclosporine (Fig. 32-1).[7]

Diplopia

Certain drugs commonly cause diplopia by leading to breakdown of a latent squint. These include benzodiazepines, tricyclic antidepressants, anticonvulsants, indomethacin, quinine, methaqualone, and fenfluramine. Rarely, diplopia may be due to an extraocular muscle palsy, gaze palsy, or internuclear ophthalmoplegia.

Nystagmus

Drug-induced nystagmus is common in hospital practice. Horizontal vestibular nystagmus may be seen in patients taking high doses of barbiturates, benzodiazepines, anticonvulsants, or other sedative and hypnotic drugs. It is a useful early sign of toxicity in patients on anticonvulsant therapy and may occur even with therapeutic doses of some of these drugs. Other drugs reported to cause nystagmus rarely include monoamine oxidase inhibitors, salicylates, gold, neostigmine, chlordiazepoxide, fenfluramine, and amitriptyline, as well as the ototoxic antibiotics and a number of other medications. Downbeat nystagmus may also be drug-induced and has been associated with administration of lithium, amiodarone, and lamotrigine, and with phenytoin toxicity.

DISORDERS OF TASTE AND SMELL

Drug-induced disorders of taste and smell are common. Many drugs cause metallic, bitter, or salty taste sensations (phantogeusia) or other distortions of taste. These include biguanides, ethambutol, vitamin D, gold, allopurinol, penicillin, metronidazole, tinidazole, lincomycin, clindamycin, terbinafine, aspirin, and phenindione. A number of other drugs may also cause a reduction or loss in taste, the perception of sweetness being most often affected, including D-penicillamine (which causes marked hypogeusia in up to 30% of patients, corrected by the administration of copper), levodopa, captopril, enalapril, etidronate, oxyfedrine, methimazole, carbimazole, thiouracil, phenylbutazone, amphotericin B, griseofulvin, terbinafine, azathioprine, salazosulfapyridine, chlormezanone, carbamazepine, and baclofen.

Distortion or loss of the sense of smell (anosmia) has been associated with many different drugs including amoxicillin/clavulanic acid, doxycycline, erythromycin, captopril, intranasal steroids, and others. In most cases the sense of taste or smell recovers with the passage of time, but in some instances the impairment is irreversible. For most of the drugs just mentioned, disturbances of taste and smell will be listed as potential adverse effects in the product information, but this will not necessarily be the case with more recently introduced therapeutic products.

SPINAL DISORDERS

An acute ischemic myelopathy can occur in heroin addicts due to vasculitis and has also been reported following accidental injection of penicillin into the superior gluteal artery. Acute cord compression may result from hemorrhage into the extradural space in patients on anticoagulants. Spinal cord compression has also been reported as a result of hyperplastic extradural adipose tissue in patients on prolonged corticosteroid therapy.

A syndrome of myeloneuropathy with sensory loss in the hands and feet, Lhermitte sign, leg weakness, spasticity, ataxia, and sphincter disturbances can occur as a result of prolonged occupational or recreational exposure to nitrous oxide, particularly in the dental profession. The condition resembles subacute combined degeneration of the spinal cord and is thought to be due to the inhibitory effects of nitrous oxide on vitamin B_{12} utilization. Recovery usually occurs after exposure to nitrous oxide is discontinued and treatment is provided with vitamin B_{12} and folate supplements. A posterior column myelopathy may also occur following intrathecal administration of methotrexate.

Spinal anesthesia can be followed by headache, nausea, vomiting, and transient neurologic symptoms such as urinary retention and pain or sensory symptoms in the lower limbs. More serious complications such as radiculopathy or cauda equina syndrome due to damage to the spinal nerve roots, and epidural hematoma or abscess can also occur, but are rare.

Intrathecal injection of methylprednisolone (Depo-Medrol) can cause an acute meningeal reaction due to the polyethylene glycol detergent in the preparation, and may present with an acute cord syndrome. Other drugs that can be toxic when administered intrathecally include baclofen, lidocaine, morphine, chymopapain, methotrexate, cytarabine, and radiologic contrast agents. Epidural injections are not usually associated with such reactions unless there is inadvertent dural puncture.

AUTONOMIC DISORDERS

Postural Hypotension

Many drugs may cause postural hypotension, resulting in dizziness, falls, or syncope; focal cerebral ischemic events sometimes occur in patients with severe cerebrovascular disease. The drugs most frequently implicated are antihypertensives, vasodilators, diuretics, tricyclic antidepressants, and levodopa.

Bladder Dysfunction

Anticholinergic drugs may cause urinary retention by inhibiting parasympathetic postganglionic cholinergic neurons, particularly if there is bladder outflow obstruction due to prostatic hypertrophy. These drugs include atropine, hyoscine, propantheline, benzhexol, benztropine, methixene, orphenadrine, dicyclomine, and belladonna derivatives. Tricyclic antidepressants and phenothiazines may also precipitate acute urinary retention because of anticholinergic effects. Other drugs that may cause urinary retention include monoamine oxidase inhibitors, disopyramide, ephedrine, salbutamol, terbutaline, and theophylline.

A number of other drugs may also interfere with control of micturition and cause urinary incontinence. These include prazosin, metoprolol, benoxaprofen, depot phenothiazines, clonazepam, phenoxybenzamine, and methyldopa.

Sexual Dysfunction

Many drugs interfere with normal sexual function, causing loss of libido, impotence, impaired ejaculation, or orgasmic dysfunction. The most common are antihypertensives, tricyclic antidepressants, monoamine oxidase inhibitors, SSRIs, major tranquilizers, antihistamines, and anticholinergics, as well as baclofen, cimetidine, clofibrate, disopyramide, dopamine agonists, and levodopa.

PERIPHERAL NEUROPATHIES

Drug-induced neuropathies account for only a small proportion of cases of peripheral neuropathy, but their importance lies in the fact that they are potentially reversible if the causative agent is identified early and withdrawn before irreversible axonal damage occurs.

Various drugs may adversely affect peripheral nerve function and cause an axonal or demyelinating neuropathy (Table 32-3). The risk of drug-induced neuropathy is higher in individuals with diabetes mellitus, alcoholism, renal or hepatic insufficiency, or a preexisting neuropathy, or those treated with more than one neurotoxic drug ("synergistic neurotoxicity"). Some drugs principally affect sensory nerve function, causing paresthesias and sensory loss whereas others, such as dapsone and gold, cause a predominantly motor neuropathy with inconspicuous or absent sensory changes. Most drugs, however, produce a mixed sensorimotor neuropathy usually manifesting initially

TABLE 32-3 ■ Drugs Associated With Development of Peripheral Neuropathy

Antineoplastics	Vinca alkaloids: vincristine, vinblastine
	Taxanes: paclitaxel, docetaxel, cabazitaxel
	Platinum compounds: cisplatin, carboplatin, oxaliplatin,
	Epothilones: eribulin, ixabepilone
	Proteasome inhibitors: bortezomib, carfilzomib, ixazomib
	Others: cytarabine, thalidomide, misonidazole, podophyllin
Antimicrobials	Isoniazid, ethambutol, ethionamide, streptomycin, fluoroquinolones, chloramphenicol, dapsone, metronidazole, voriconazole, fluconazole, stibogluconate, suramin
Antirheumatics	Chloroquine, hydroxychloroquine, etanercept, infliximab, adalimumab, colchicine, D-penicillamine
Immune Therapies	Tacrolimus, leflunomide, interferon-alpha and beta, immune checkpoint inhibitors
Cardiovascular Drugs	Amiodarone, perhexiline, simvastatin, atorvastatin, disopyramide, hydralazine, flecainide, enalapril, captopril
Psychotropics/Sedatives	Phenelzine, lithium, tricyclics, perazine, glutethimide, methaqualone
Other Drugs	Levodopa, disulfiram, pyridoxine, dichloroacetate, phenytoin, streptokinase

with sensory symptoms, followed by motor symptoms later if the drug is continued. In addition to paraesthesias, myalgia and cramps are early symptoms in some cases. The tendon stretch reflexes are preserved in the early stages but are usually depressed or lost in more advanced cases.

Antineoplastic Drugs

Chemotherapy-induced peripheral neuropathy is an important complication of treatment particularly with the vinca alkaloids, platinum compounds, and taxanes, which cause dose-dependent (and dose-limiting) neurotoxicity.[13] Vincristine and other vinca alkaloids, which bind β-tubulin and prevent its polymerization into microtubules, are particularly neurotoxic. Most patients treated with these drugs for long enough will develop a sensorimotor polyneuropathy with early loss of tendon reflexes and sometimes autonomic symptoms. Muscle cramps may be prominent in the early stages, and some patients also develop a painful proximal myopathy. Recovery may occur if the drug is stopped or the dose is reduced, but mild sensory symptoms and areflexia often persist. In some patients treated with these drugs, symptoms of neuropathy may not develop until after the treatment is completed or may progress despite cessation of treatment, a phenomenon referred to as "coasting."

The platinum compounds are all potentially neurotoxic as well as ototoxic, and cause a painful sensory neuropathy with proprioceptive impairment and sensory ataxia. Cisplatin and carboplatin cause a dorsal root ganglion neuronopathy rather than a dying-back axonopathy. Oxaliplatin, which interferes with axonal ion conductance, causes transient sensory symptoms after intravenous administration, but a persisting neuropathy may develop after repeated infusions.

The taxanes (paclitaxel, docetaxel, and cabazitaxel), which lead to aggregation of microtubules, can cause a predominantly sensory or sensorimotor axonal neuropathy and principally affect large-diameter myelinated sensory and motor fibers. Coadministration of other neurotoxic drugs such as cisplatin further increases the risk of neuropathy. The recently introduced epothilone group of drugs, which also affect microtubules, may also cause peripheral neuropathy. Eribulin and ixabepilone, which are used to treat breast cancer, can both cause an axonal sensorimotor peripheral neuropathy.

The proteasome inhibitor bortezomib, which is used to treat multiple myeloma, presents with a painful length-dependent predominantly axonal sensory neuropathy in about 30 percent of patients, with an associated autonomic neuropathy in 10 to 15 percent of cases. The neuropathic effects of bortezomib can be reduced by subcutaneous administration and may be reversed with cessation of the drug or dose reduction. A small proportion of patients develop a severe polyradiculoneuropathy, which is thought to be immune mediated. The newer generation proteasome inhibitors, carfilzomib and ixazomib, appear to be less neurotoxic and have a lower incidence of neuropathy.

Long-term treatment with thalidomide, which is used for the treatment of myeloma, can cause a predominantly sensory peripheral neuropathy thought to be due to the antiangiogenic effects of the drug. Newer formulations of the drug, lenalidomide and pomalidomide, appear to be less neurotoxic.

Misonidazole and other compounds related to metronidazole are used as radiosensitizing agents in cancer therapy and may induce a sensory neuropathy. Podophyllin derivatives, which have been used to treat disseminated malignancy and are also constituents of certain laxative preparations and topical agents, may cause a peripheral neuropathy or myeloneuropathy. A severe demyelinating peripheral neuropathy has also been reported after high-dose cytarabine therapy in leukemia patients.

Antimicrobial Agents

Historically, the best-known examples of antimicrobial-induced neuropathy are the mixed sensorimotor neuropathy caused by isoniazid, which interferes with pyridoxine metabolism and can be prevented by coadministering vitamin B_6 supplements, and the sensory or sensorimotor neuropathy or optic neuropathy caused by ethambutol. Ethionamide and streptomycin can also rarely cause a peripheral neuropathy, but this is less frequent than the ototoxic effects of streptomycin. Peripheral neuropathy was a recognized complication of sulfonamide treatment in the past, but none of the drugs in current use have this effect. A sensorimotor or motor peripheral neuropathy is a well-documented complication of treatment with nitrofurantoin, especially in patients with renal insufficiency. There have been reports of a reversible neuropathy in patients on prolonged metronidazole therapy. The risk of peripheral neuropathy is increased with oral intake of fluoroquinolone antibiotics, particularly in elderly men, but not with amoxicillin-clavulanate.[14]

The triazole antifungal agents voriconazole and itraconazole have been reported to cause a sensorimotor neuropathy in conjunction with neurotoxic chemotherapy, and in the treatment of invasive aspergillosis and fluconazole-resistant *Candida* infections. This has also been described in leukemia patients not receiving neurotoxic chemotherapy.

Dapsone, used in the treatment of leprosy and certain dermatologic conditions, may cause a predominantly motor neuropathy after prolonged high-dose therapy. Suramin, when used to treat trypanosomiasis or onchocerciasis, may cause a dose-related axonal sensorimotor neuropathy with lamellar inclusions in dorsal root ganglia and Schwann cells, and may mimic the Guillain–Barré syndrome clinically. Sodium stibogluconate has also been associated with the development of peripheral neuropathy when used in the treatment of leishmaniasis.

Antirheumatic Drugs

Peripheral neuropathy is a well-recognized complication of gold therapy in rheumatoid arthritis. Motor involvement is usually prominent and sensory symptoms are inconspicuous. The onset may be abrupt and the progression rapid, and in some cases may mimic Guillain–Barré syndrome, particularly in patients who develop facial diplegia and elevated cerebrospinal fluid protein levels. A sensory or mixed neuropathy has also been reported in patients with rheumatoid arthritis treated with leflunomide.

Chloroquine may cause a mild sensorimotor neuropathy or more severe neuromyopathy. A neuropathy may occur rarely in patients treated with D-penicillamine, and Guillain–Barré syndrome has been reported to occur. A mixed sensorimotor neuropathy sometimes develops in patients treated with colchicine for long periods and is often associated with a proximal myopathy.

Several types of neuropathy have been described with the TNF-α inhibitors etanercept and infliximab, including Guillain–Barré syndrome, Miller Fisher syndrome, chronic inflammatory demyelinating neuropathy, multifocal motor neuropathy with conduction block, mononeuritis multiplex, and axonal sensory or sensorimotor polyneuropathy. The pathogenesis is thought to involve a T-cell and humoral immune attack against peripheral nerve myelin antigens, inhibition of axonal signaling functions, and vasculitis-induced ischemia. Adalimumab may also be associated with a peripheral neuropathy; multifocal motor neuropathy with conduction block and acute bilateral phrenic neuropathy have been reported.

Cardiovascular Drugs

A demyelinating sensorimotor polyneuropathy is well documented in patients treated with the antiarrhythmic agent amiodarone and in the past also occurred in patients treated with the coronary vasodilator perhexiline, which is no longer in clinical use. Streptokinase has been associated with the development of Guillain–Barré syndrome. Peripheral neuropathy has also been reported rarely with disopyramide, hydralazine, flecainide, enalapril, and captopril.

Cholesterol-Lowering Agents

Although peripheral neuropathy was not detected in the initial large statin trials, a number of subsequent reports have highlighted the development of various types of neuropathy in small numbers of patients treated with various statin drugs. Most are reports of an axonal sensorimotor polyneuropathy, but a definite causal association is not established. In Australia, the National Adverse Drug Reactions Advisory Committee received reports between 1993 and 2005 of 281 patients with peripheral neuropathy or symptoms consistent with a neuropathy that had been attributed to statins. Most of these were associated with simvastatin or atorvastatin and, less frequently, pravastatin and fluvastatin. Recovery occurred in about 50 percent of cases after stopping the drug, but symptoms persisted for months or even years in some cases. Population-based studies in the United Kingdom and Denmark found a greater risk of having peripheral neuropathy in patients taking statins than in controls. However, the confounding effects of glucose intolerance and hyperlipidemia could not be excluded in these studies, and in the Fremantle Diabetes Study of nearly 1,300 patients the risk of neuropathy was actually lower in diabetics treated with statins and fibrates.[15]

Hypnotic and Psychotropic Drugs

There have been occasional reports of neuropathy developing in patients taking phenelzine, methaqualone, glutethimide, imipramine, amitriptyline, lithium carbonate, and perazine.

Levodopa

There is increasing awareness of the development of peripheral neuropathy in patients with Parkinson disease treated with levodopa, with up to 30 percent of patients on oral levodopa being affected and 42 percent of patients on levodopa/carbidopa intestinal gel infusion therapy.[16] In patients on oral therapy the neuropathy is usually a slowly progressive small-fiber neuropathy, whereas in patients on gel infusion therapy it can be more acute or subacute.

Other Drugs

Various other drugs have occasionally been implicated in causing a neuropathy. A mild peripheral neuropathy can occur in patients on long-term treatment with phenytoin but is rarely symptomatic. Disulfiram, used in the treatment of alcoholism, may cause an axonal sensorimotor polyneuropathy, as well as an optic neuropathy.

There have been a number of reports of axonal polyneuropathy and trigeminal neuropathy developing in patients with hepatitis C treated with interferon-alpha; more recently, cases of Guillain–Barré syndrome have been reported with pegylated interferon-alpha, which is now more commonly used for the treatment of hepatitis C infection.

A number of older drugs including streptokinase, D-penicillamine, captopril, danazol, zimeldine, and gangliosides have been associated with the development of Guillain–Barré syndrome. A demyelinating neuropathy with features of chronic inflammatory demyelinating polyneuropathy has occurred in patients treated with tacrolimus and interferon-alpha. Peripheral neuropathy has also been reported in a number of patients with multiple sclerosis treated with interferon-beta.

Chronic intake of high doses of pyridoxine as a dietary supplement may cause a severe sensory polyneuropathy, and paresthesias may develop even in some patients taking conventional doses of this vitamin. Dichloroacetate may bring on or worsen peripheral neuropathy in patients with the syndrome of mitochondrial myopathy, lactic acidosis, and stroke-like episodes (MELAS).

NEUROMUSCULAR TRANSMISSION DISORDERS

Various drugs can interfere with neuromuscular transmission by causing a postsynaptic block or through a presynaptic effect on transmitter release, as occurs with botulinum toxin (Table 32-4). The most common clinical manifestation is the postoperative respiratory depression that occurs in patients being treated with aminoglycoside antibiotics or other drugs that can potentiate the effects of muscle relaxants used during anesthesia.

Many of the drugs listed in Table 32-4 can also unmask or aggravate a pre-existing myasthenic disorder by reducing the safety factor for neuromuscular transmission, and should therefore be avoided or used with caution in myasthenic patients. In particular, all antibiotics should be used with caution in myasthenic patients. Based on current recommendations, fluoroquinolones (ciprofloxacin and norfloxacin), macrolides (azithromycin and erythromycin), ketolides (especially telithromycin), aminoglycosides, and polymyxins are regarded as having the highest risk of aggravating myasthenia

TABLE 32-4 ■ Drugs that May Interfere With Neuromuscular Transmission

Antibiotics

Aminoglycosides
Polymyxins
Fluoroquinolones
Macrolides
Ketolides
Ampicillin
Imipenem
Clindamycin
Lincomycin

Anesthetic Agents

Muscle relaxants
Diazepam
Ketamine
Propanidid
Lidocaine
Procaine

Cardiovascular Drugs

Statins
β_2-Adrenergic blockers
Quinidine
Procainamide
Verapamil

Immune Therapies

Glucocorticoids
Corticotrophin
α-Interferon
Immune checkpoint inhibitors

Anticonvulsants

Phenytoin
Trimethadione
Gabapentin
Barbiturates

Antirheumatics

Chloroquine
D-Penicillamine

Antipsychotics

Phenothiazines
Lithium

Other Drugs

Botulinum toxin
Cholinesterase Inhibitors
Anticholinergics
Quinine
Thyroxine
Diuretics
Oxytocin
Carnitine
Deferoxamine
Ritonavir
Magnesium salts

and should all be avoided, whereas cephalosporins and penicillins, with the exception of ampicillin, are generally considered to be safe. Sulfonamides, clindamycin, lincomycin, imipenem, and voriconazole may also interfere with neuromuscular transmission and aggravate the symptoms of myasthenia.

Deterioration of myasthenia, and rarely even myasthenic crisis, may occur following therapeutic botulinum toxin injections, particularly when high cumulative doses are administered. Other drugs that should be used with caution in myasthenic patients include β-blockers, procainamide, quinine, quinidine, anticonvulsants, lithium, lidocaine and other local anesthetics administered intravenously, phenothiazines, anticholinergics, diuretics, and thyroxine. Statins have been implicated in the development of or aggravation of autoimmune myasthenia gravis in small case series and case reports, but a definite causal relationship has yet to be established. Although glucocorticoids are commonly used in the treatment of myasthenia, at high doses they may cause a significant exacerbation of symptoms when first commenced and such patients should therefore be kept under close observation when treatment is initiated.

Autoimmune myasthenia may develop in patients treated with α-interferon or on long-term treatment with D-penicillamine or thiopropine. These patients usually have acetylcholine receptor (AChR) antibodies in the serum, and rarely muscle-specific kinase (MUSK) antibodies. Since the introduction of cancer immunotherapy and the use of PD-1 immune checkpoint inhibitors there have also been increasing reports of the development of myasthenia, as well as other autoimmune disorders, in cancer patients treated with pembrolizumab, novolumab, and ipilimumb.[17]

MUSCLE DISORDERS

A variety of drugs may cause a myopathy or muscular symptoms through direct toxic effects on the skeletal muscles (Table 32-5).[18] In addition, a number of other drugs that are not intrinsically myotoxic may cause myopathy and weakness through an immune mechanism or by inducing severe hypokalemia or muscle ischemia, or cause rhabdomyolysis as a result of muscle compression during prolonged periods of unconsciousness after a drug overdosage ("crush syndrome").

Cholesterol-Lowering Agents

Myopathy is an important side effect of treatment with the 3-hydroxy-3-methylglutaryl—coenzyme A reductase (HMGCR) inhibitors (statins) and fibrate drugs that interfere with the biosynthesis of cholesterol. The risk of developing myopathy was shown to be increased 8-fold in patients on statins and 42-fold in patients on fibrates in a case-control study in the United Kingdom. A myopathy may also develop in patients treated with ezetimibe, which blocks cholesterol absorption, and in patients on high doses of nicotinic acid.

TABLE 32-5 ■ Drugs Associated With the Development of a Myopathy

Lipid-lowering Agents
- Statins
- Fibrates
- Ezetimibe
- Nicotinic acid

Antirheumatics
- Chloroquine
- Hydroxychloroquine
- Colchicine
- D-Penicillamine

Glucocorticoids
- Prednisone
- Methylprednisolone
- Dexamethasone
- Inhaled steroids

Immune Therapies
- Immune checkpoint inhibitors
- TNF-α inhibitors
- α-Interferon
- Tacrolimus
- Cyclosporine

Antineoplastic Agents
- Vincristine
- Bevacizumab
- Selumetinib

Cardiovascular Drugs
- Amiodarone
- Cardiac glycosides
- Perhexiline
- Hydralazine
- Scillaren

Hormonal Therapies
- Thyroxine
- Leuprolide
- Teriparatide
- Propylthiouracil

Other Drugs
- Antiretrovirals
- Clevudine
- Emetine
- Etretinate
- Proton-pump inhibitors
- Biotin
- ε-Aminocaproic acid
- Streptokinase
- Glycyrrhizic acid
- Germanium

Statins can cause a spectrum of myotoxic effects, ranging from asymptomatic hyperCKemia to a symptomatic necrotizing myopathy with myalgia and muscle weakness (Fig. 32-2), and the most extreme form, a syndrome of severe rhabdomyolysis and myoglobinuria that is potentially lethal. The risk of myopathy is greater with the lipophilic statins such as simvastatin, atorvastatin, and lovastatin, and is further increased by coadministration of a fibrate (e.g., gemfibrozol) or drugs that compete with or inhibit the CYP3A4 enzyme system. These include cyclosporine, macrolide antibiotics, calcium-channel blockers, SSRI antidepressants, azole antifungal agents, as well as grapefruit juice, which should be avoided or restricted during statin therapy. Acute rhabdomyolysis is the most severe form of statin myopathy and is rare, but in the past was associated particularly with cerivastatin, which was withdrawn from the market in 2001 after the occurrence of over 100 fatal cases of rhabdomyolysis. Other risk factors for statin myotoxicity include age, dose escalation, diabetes, hypothyroidism, renal failure, and hepatobiliary disease. Pharmacogenetic factors may also predispose to susceptibility. In the majority of cases of statin myopathy, there is progressive improvement in muscle symptoms and complete recovery usually occurs within 2 to 3 months following drug withdrawal.

In patients whose muscle symptoms fail to improve or continue to progress after withdrawal of the statin, further investigations including a muscle biopsy should be performed as statins may rarely induce an antibody-mediated form of necrotizing autoimmune myopathy (NAM), which is associated with the presence of circulating anti-HMGCR antibodies.[19] The muscle biopsy in this condition shows myofiber necrosis and regeneration, with upregulated MHC-I expression and deposition of the C5b9 membrane attack complex of complement, and a sparse or absent inflammatory infiltrate. The phenotypic spectrum of anti-HMGCR myopathy is now known to also include pediatric patients and young adults not previously exposed to statins, as well as a more chronic form of myopathy that may resemble limb-girdle muscular dystrophy. Treatment of anti-HMGCR NAM consists of withdrawing the responsible statin and initiating immunotherapy, the most frequently used agents being glucocorticoids, methotrexate, azathioprine, or mycophenolate, and in resistant cases rituximab and intravenous immunoglobulins. In most cases, more than one form of immunosuppression is required to achieve remission, and relapse is common after withdrawal or weaning of immunotherapy.

Statins may also unmask a previously unrecognized myopathy, such as mitochondrial or other metabolic myopathies, and may aggravate symptoms in patients with other myopathies.

Inflammatory Myopathies

A number of drugs may initiate an immune-mediated inflammatory myopathy. The best known are D-penicillamine and interferon-alpha, both of which may cause either polymyositis or dermatomyositis. More recently the main drugs implicated are the TNF-α inhibitors, particularly etanercept and adalimumab, and statins. In

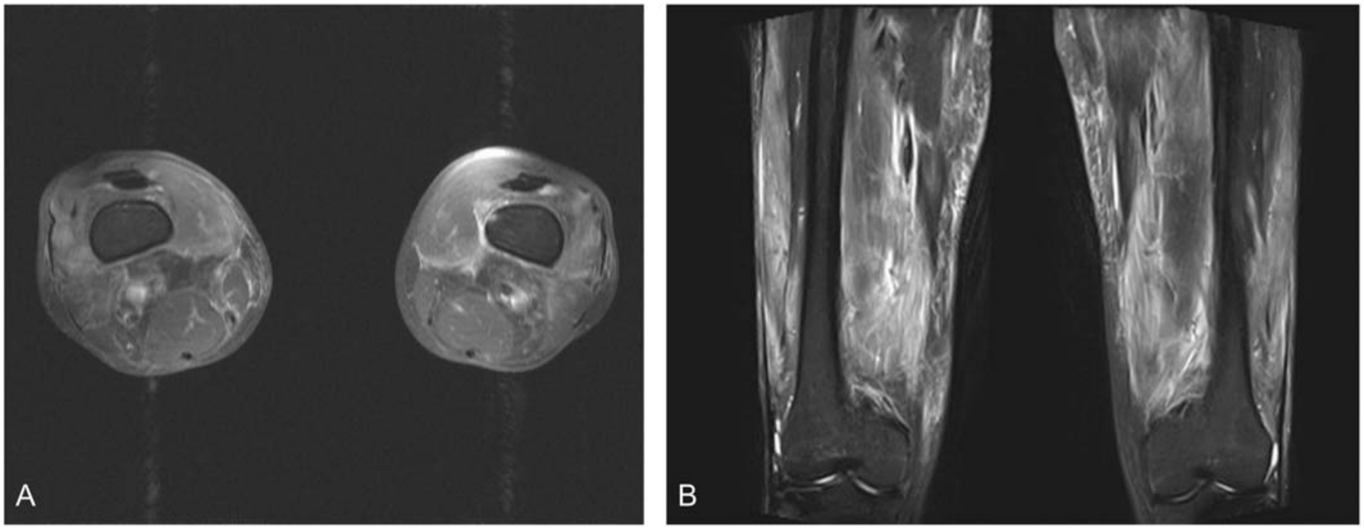

FIGURE 32-2 ■ Axial (*A*) and coronal (*B*) MRI of the proximal lower extremities showing extensive signal change in the quadriceps muscles in a 54-year-old man with a necrotizing myopathy that developed after he started atorvastatin.

the case of statins, in addition to NAM, dermatomyositis and polymyositis have been reported. There are reports of polymyositis, dermatomyositis, and especially NAM developing in patients treated with the PD-1 immune checkpoint inhibitors pembrolizumab, ipilimumab, and nivolumab.[17]

A condition referred to as macrophagic myofasciitis was first recognized in the 1990s in France, where over 130 cases were documented, and was also reported from other countries. It was characterized by diffuse myalgia, arthralgia, and fatigue, with a good response to corticosteroid therapy, and is now thought to have been caused by intramuscularly injected vaccines containing aluminum hydroxide. A syndrome of eosinophilic myositis and fasciitis associated with severe myalgia, edema, and induration of the skin was also reported in the early 1990s in patients taking a contaminated preparation of L-tryptophan as a hypnotic (the eosinophilia-myalgia syndrome).

An interstitial form of myositis characterized clinically by muscle pain, stiffness, and mild weakness has been reported rarely in patients treated with a number of drugs including procainamide, hydralazine, phenytoin, levodopa, cimetidine, leuprolide, or propylthiouracil.

Acute Rhabdomyolysis

Acute rhabdomyolysis is the most serious form of drug-induced myopathy and has been associated with statin treatment and a number of other drugs. It may also occur after self-administration of heroin, cocaine, amphetamines, ecstasy, or LSD, as well as with alcohol intoxication, drug-induced coma, seizures, dyskinesias, or the neuroleptic malignant syndrome (discussed earlier). Severe muscle pain, tenderness, and weakness typically develop over a period of 24 to 48 hours, often with marked limb swelling and in some cases the development of a secondary compartment syndrome. The serum CK is markedly elevated, and myoglobinuria is an early feature, sometimes leading to acute oliguric renal failure. Muscle biopsy usually shows widespread muscle fiber necrosis and often regeneration. The prognosis for recovery is generally good, but some more severely affected patients may die as a result of multiple organ failure. The management of patients with acute rhabdomyolysis is primarily supportive, with monitoring of renal function and fluid and electrolyte balance and early treatment of any metabolic derangements. Monitoring of compartment pressures is important in patients with muscle swelling as some patients require fasciotomy and muscle decompression.

Mitochondrial Myopathies

A myopathy with ragged-red fibers, paracrystalline mitochondrial inclusions, and depletion of muscle mtDNA has occurred in patients with acquired immune deficiency syndrome (AIDS) on long-term treatment with the antiretroviral agent zidovudine. It is characterized by myalgia, fatigue, proximal or generalized weakness, and raised serum CK level. Highly active antiretroviral (HAART) therapy, including the nucleoside analogues didanosine and stavudine, has also been reported to cause a mitochondrial myopathy with a clinical phenotype resembling chronic progressive external ophthalmoplegia.

A slowly progressive mitochondrial myopathy with marked serum CK elevation was originally reported in Korean patients with hepatitis B infection treated with the pyrimidine nucleoside analogue clevudine.

A mitochondrial myopathy has also been reported in patients taking germanium, which is a constituent of a number of dietary supplements and elixirs. Statin therapy may unmask a previously undiagnosed mitochondrial myopathy.

Potassium-Related Myopathies

Severe weakness with hypotonia, depressed tendon reflexes, and marked serum CK elevation may develop in patients with severe hypokalemia as a result of treatment with diuretics or fluoroprednisolone-containing nasal sprays, or as a result of purgative abuse or the consumption of large quantities of licorice or licorice extracts, which are ingredients of some traditional Chinese drugs and contain the potent mineralocorticoid analogue glycyrrhizic acid. Hypokalemia and myopathy may also complicate treatment with amphotericin B due to the development of renal tubular acidosis. Profound muscle weakness may occur in patients taking potassium-retaining diuretics who develop hyperkalemia.

Glucocorticoid Myopathy

A myopathy characterized by selective atrophy of type IIb myofibers is a frequent complication of prolonged treatment with glucocorticoids and is probably the most common drug-induced myopathy encountered in clinical practice. A symptomatic myopathy is more likely to develop in patients treated with the fluorinated glucocorticoids triamcinolone, betamethasone, and dexamethasone, but may also occur in patients taking prednisone or prednisolone (in doses exceeding 10 mg per day) for long periods. Those taking daily doses of 40 mg or more are at particular risk of developing a myopathy, whereas an alternate-day regimen is considered to be protective. The elderly and patients with cancer or other chronic diseases and immobility are particularly predisposed to develop a myopathy on glucocorticoids. A more acute form of glucocorticoid myopathy in which there is myofiber necrosis and elevated serum CK levels may also occur, usually in an intensive care setting in patients receiving high doses of intravenous glucocorticoids.

The muscles of the pelvic girdle and thighs are most severely affected in the chronic myopathy, whereas the weakness is more generalized in acute glucocorticoid myopathy. Muscles innervated by the cranial nerves are usually spared, but involvement of the laryngeal muscles leading to dysphonia can occur in patients using inhaled corticosteroids such as beclomethasone and fluticasone. Diaphragmatic weakness may develop in asthmatic patients taking corticosteroids, and weakness of the respiratory muscles has been reported in patients with chronic obstructive pulmonary disease and in cancer patients treated with corticosteroids. Serum CK levels are usually normal, and if elevated should suggest the possibility of an inflammatory or other type of myopathy.

Glucocorticoid myopathy is usually reversible if the drug is stopped or the dose reduced, or by switching to an alternate-day regimen or nonfluorinated glucocorticoid. Muscle atrophy and weakness can be prevented, at least in part, by a high-protein diet and regular program of physical exercise. Growth hormone and insulin-like growth factor-1 may also be protective.

Acute Quadriplegic Myopathy

Acute quadriplegic myopathy, also referred to as critical illness myopathy, occurs in critically ill patients such as severe asthmatics or organ-transplant recipients. It also occurs in patients with severe sepsis undergoing prolonged periods of mechanical ventilation and treatment with high doses of intravenous glucocorticoids and nondepolarizing neuromuscular blocking agents in the intensive care unit. There is profound generalized muscle weakness, hypotonia, and depressed tendon reflexes, and respiratory muscle weakness often leads to difficulties in weaning from the respirator. The serum CK level is usually moderately elevated, but may be normal. Muscle biopsy shows atrophy and necrosis of muscle fibers, with loss of myosin ATPase activity and a highly characteristic pattern of selective loss of myosin filaments in sarcomeres on electron microscopy. The condition has been referred to as an acquired myosinopathy. Electrophysiologic studies show reduced amplitude of compound muscle action potentials and reduced muscle excitability to direct electrical stimulation. Such studies are performed to exclude other conditions that may result in a similar clinical syndrome, such as critical illness neuropathy, Guillain–Barré syndrome, or a neuromuscular transmission disorder.

Gradual recovery usually occurs over a period of several months and is enhanced by an intensive program of physiotherapy.

Autophagic Myopathies

A number of amphiphilic cationic drugs cause autophagic degeneration and phospholipid accumulation in muscle and other tissues. These include chloroquine and hydroxychloroquine, which can cause a painless proximal myopathy or neuromyopathy after prolonged administration, and amiodarone, perhexiline, and colchicine, which can cause both a myopathy and a peripheral neuropathy. Immunohistochemistry for microtubule-associated protein light-chain 3 and p62 can facilitate tissue-based diagnosis of drug-induced autophagic vacuolar myopathies without the need for electron microscopy, making the diagnosis potentially more accurate and efficient.

Malignant Hyperthermia

Malignant hyperthermia is a condition in which susceptible individuals develop a potentially lethal state of severe generalized muscular rigidity, hyperpyrexia, tachycardia, metabolic acidosis, and myoglobinuria when exposed to certain volatile anesthetic agents such as halothane or other drugs such as succinylcholine during general anesthesia. Susceptibility is transmitted as an autosomal dominant trait and may be associated with either a clinically apparent or a subclinical myopathy. Mutations in the ryanodine receptor gene (*RYR1*) or the *CACNA1S* gene that encodes the α_1-subunit of the voltage-gated dihydropyridine receptor have been identified in only 50 to 70 percent of affected families, and genetic screening is as yet not sufficiently reliable to identify all at-risk individuals. The most reliable method is still the in vitro muscle contracture test to demonstrate abnormal sensitivity of muscle tissue when exposed to halothane and caffeine. A similar susceptibility to anesthetic reactions may also occur in some patients with Duchenne or Becker muscular dystrophy, myotonia congenita, myotonic dystrophy, core myopathies, and hypokalemic periodic paralysis.

The malignant hyperthermia crisis is thought to be due to an intrinsic abnormality of the excitation–contraction coupling mechanism in skeletal muscle, as a result of which exposure to anesthetic agents leads to the excessive release of calcium ions from the sarcoplasmic reticulum, causing sustained myofibrillar contraction. Management involves the urgent administration of dantrolene, body cooling, correction of fluid and electrolyte balance, and prompt treatment of complications.

Drug-Induced Myotonia

A number of drugs may induce myotonia in humans or experimentally in animals. These include the early-generation lipid-lowering agents clofibrate, triparanol, zuclomiphene, and 20,25-diazacholesterol. In addition, certain drugs may exacerbate myotonia in patients with a pre-existing genetic form of myotonia or unmask previously undetected myotonia. These include depolarizing muscle relaxants such as suxamethonium, which may markedly exacerbate myotonia during anesthesia, as well as β_2-adrenergic antagonists (e.g., propranolol and pindolol) and β_2-agonists (e.g., fenoterol and ritodrine). A number of diuretics, including acetazolamide, furosemide, mersalyl, and ethacrynic acid are known to induce myotonia in animals, and should be used with caution in patients with genetic forms of myotonia.

Myalgia, Cramps, and Twitches

Many different drugs including statins, fibrates, diuretics, β-adrenergic agonists, calcium-channel blockers, cytotoxic drugs, colchicine, lithium, cyclosporine, procainamide, and gold compounds may cause muscle pain and cramps that are reversible if the drug is withdrawn. In some cases, the serum CK activity may be transiently elevated. Similar symptoms may occur in patients with drug-induced myotonia, and may also be the early symptoms of a more severe necrotizing myopathy. Muscle pain and fasciculations are commonly associated with the use of suxamethonium during anesthesia. Muscle twitching (fasciculations and myokymia) has also been reported in patients treated with gold or D-penicillamine, and rarely rippling muscle disease with statins.

Other Rare Drug-Induced Myopathies

Muscle weakness is a common side effect of treatment with emetine in patients treated for amebiasis, and a severe myopathy has also been reported in individuals using ipecac syrup, which contains emetine, as an emetic agent. A proximal myopathy with myalgia, fatigability, and marked elevation of serum CK has been reported with use of large quantities of the cough-suppressant codeine linctus, one of the constituents of which is squill, which contains the cardiac glycosides scillaren A and B that inhibit the sodium–potassium pump. In the past, a severe necrotizing myopathy was a known complication of treatment with the antifibrinolytic agent ε-aminocaproic acid.

There are also rare reports of myopathy associated with the use of omeprazole and other proton-pump inhibitors, tetracyclines, griseofulvin, sulfasalazine, rifampicin, mercaptopropionyl glycine, vidarabine, ethchlorvynol, finasteride, etretinate, and isotretinoin. The protein kinase inhibitor selumetinib has been reported to cause a reversible focal myopathy of the neck extensor muscles. The recombinant human parathyroid hormone teriparatide, which is used to treat postmenopausal osteoporosis, can cause a reversible proximal lower-limb myopathy involving the gluteal muscles. A reversible myopathy with muscle lipid storage and weakness of the neck extensor muscles has also been associated with high-dose biotin administration.

Severe muscle fibrosis and contractures may occur as a result of repeated intramuscular injections in illicit drug abusers or rarely after prolonged courses of antibiotic injections.

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CHAPTER

33

Alcohol and the Nervous System

ROBERT O. MESSING

ALCOHOL INTOXICATION AND WITHDRAWAL
- Intoxication
- Alcohol Withdrawal Syndromes

DISORDERS OF COGNITION
- Alcohol-Related Dementia
- Wernicke Encephalopathy
- Korsakoff Syndrome
- Pellagra
- Marchiafava—Bignami Disease
- Hepatocerebral Disorders

ALCOHOLIC CEREBELLAR DEGENERATION

CENTRAL PONTINE AND EXTRAPONTINE MYELINOLYSIS

ALCOHOL-RELATED NEUROPATHY

ALCOHOL-RELATED MYOPATHY
- Acute Necrotizing Myopathy
- Chronic Myopathy

ALCOHOL AND STROKE

> *Who could have foretold, from the structure of the brain, that wine could derange its functions?*
>
> Hippocrates (c. 460 BCE to 370 BCE)

Alcohol is the most commonly used recreational psychoactive substance worldwide. While moderate drinking may be beneficial to cardiovascular health, excessive use can result in alcohol use disorder, which is characterized by compulsive alcohol use despite harmful consequences and is often accompanied by serious complications resulting from alcohol toxicity and nutritional deprivation. In the nervous system, excessive alcohol consumption can damage virtually every level of the neuraxis (Fig. 33-1). Despite its protean nature, alcohol-associated neurologic disease often involves select anatomic structures or cell populations, suggesting that multiple, discrete pathophysiologic processes are involved.

ALCOHOL INTOXICATION AND WITHDRAWAL

Intoxication

In persons who drink alcohol infrequently, early signs of intoxication occur at blood alcohol concentrations less than 50 mg/dL (11 mmol/L) and include relaxation, loss of social inhibitions, increased talking, and impairment in some skilled tasks.[1] Ataxia, nystagmus, slurred speech, impaired judgment, and changes in mood and behavior generally occur at blood alcohol levels above 100 mg/dL (22 mmol/L) and are followed by central nervous system depression as blood levels increase. Amnesia for all or part of a drinking episode (“blackout”) may occur without loss of consciousness at blood levels above 140 mg/dL. Blood levels above 300 mg/dL (65 mmol/L) can produce coma, hyporeflexia, respiratory compromise, and hypotension. Although the behavioral effects of alcohol generally correlate with blood concentrations, tolerance can greatly modify the clinical response to a specific blood level. Acute tolerance develops even during a single bout of drinking and can cause the drinker to be unaffected at blood alcohol concentrations higher than those at which intoxication previously developed. In people who drink heavily, the degree of tolerance can be extensive, permitting sobriety at blood concentrations above 120 mg/dL and survival above 700 mg/dL.[1]

Alcohol Withdrawal Syndromes

In approximately 8 percent of people hospitalized for alcohol use disorder, characteristic signs of alcohol

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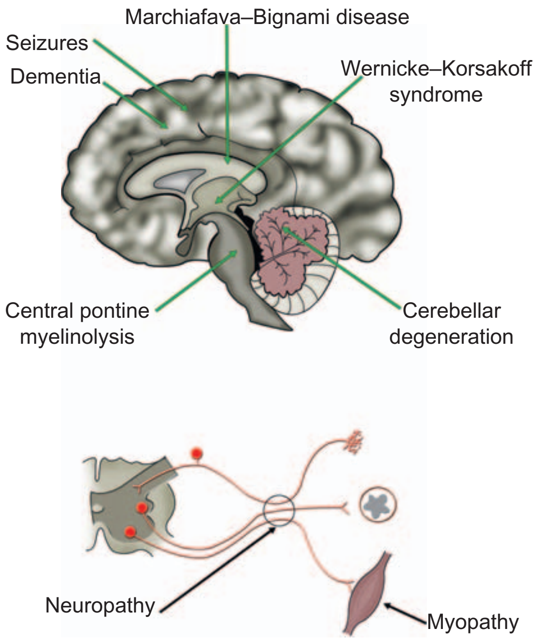
Marchiafava–Bignami disease
Seizures
Dementia
Wernicke–Korsakoff syndrome
Central pontine myelinolysis
Cerebellar degeneration
Neuropathy
Myopathy

FIGURE 33-1 ■ Alcohol-related disorders affecting different levels of the neuraxis.

withdrawal syndrome follow 1 to 3 days after abrupt cessation of heavy drinking.[2] Generalized tremor is a common early sign and resembles an accentuated physiologic tremor. It is often accompanied by insomnia, headache, and autonomic hyperactivity with increased arousal, tachycardia, diaphoresis, and flushing. These signs usually begin within 8 hours after cessation of drinking, peak at 72 hours, and resolve after 5 to 7 days.

Seizures may also occur shortly after chronic drinking is discontinued.[2] Alcohol withdrawal seizures are usually associated with a history of daily alcohol consumption, but briefer drinking sprees may also culminate in seizures following cessation. Generalized tonic-clonic seizures are most common; focal seizures suggest an etiology other than alcohol withdrawal, although alcohol can lower the seizure threshold in a patient otherwise predisposed to focal seizures. The majority of seizures occur 6 to 48 hours after cessation of drinking. Approximately 60 percent of patients have more than one seizure, but usually less than four, over a period of less than 12 hours. Status epilepticus may occur in up to 5 percent. More than half of withdrawal seizures are associated with underlying epilepsy, structural brain lesions, or concurrent use of other drugs.

In patients with repeated seizures in the setting of alcohol withdrawal, benzodiazepines (e.g., diazepam, chlordiazepoxide, and lorazepam) prevent seizure recurrence, but the evidence is not adequate to support the use of nonbenzodiazepine anticonvulsants. Status epilepticus that is suspected to be due to alcohol withdrawal is a medical emergency and should be treated with anticonvulsants in the same fashion as status epilepticus due to any other etiology, beginning with doses of benzodiazepines. It is important to recognize that alcoholics are at risk for a variety of other treatable conditions that may cause status epilepticus, including occult head trauma, meningitis, hypoglycemia, hyponatremia, and other drug ingestions.

Approximately 20 percent of patients become delirious 2 to 5 days after signs of alcohol withdrawal begin, and in 3 to 5 percent of patients hospitalized for alcohol withdrawal, the syndrome of delirium tremens develops with marked confusion, hallucinations, tremor, hyperpyrexia, and sympathetic hyperactivity. The risk of developing delirium tremens is higher in alcoholics with heavy daily alcohol intake, prior alcohol withdrawal seizures or delirium, decreased serum chloride and potassium concentrations, elevated serum levels of alanine aminotransferase and γ-glutamyltransferase, thrombocytopenia, and findings of tachycardia (≥100 bpm), ataxia, and polyneuropathy on admission.[2] The major threat to life is from associated illnesses or injuries, hyperthermia, dehydration, hypotension, arrythmias, and complications of seizures. Although initial studies reported mortality rates as high as 15 percent, rates with current methods of detection and treatment have declined to 1 percent or less.[2] A variety of sedatives, anticonvulsants, sympatholytics, and neuroleptics have been administered to patients with alcohol-withdrawal delirium, usually in uncontrolled trials. Several double-blind studies have suggested that benzodiazepines are effective in controlling the symptoms of alcohol withdrawal. Benzodiazepines and barbiturates are better than neuroleptics in reducing mortality from the delirium associated with alcohol withdrawal and should be used preferentially.

The dose of medication required to control alcohol-withdrawal symptoms can vary greatly among different patients and over time in the same patient. Three treatment approaches have been described.[2] The loading dose approach uses high doses of a long-acting benzodiazepine (e.g., 10 to 20 mg of diazepam every 1 to 2 hours) until the patient is sedated and then allows for tapering through endogenous clearance mechanisms. However, because high doses may cause respiratory depression, vital signs must be carefully monitored with each loading dose to avoid benzodiazepine toxicity, especially in patients with liver disease. In the second approach repeated fixed doses at regular intervals are administered; this strategy can be particularly useful when it is difficult to assess and monitor progression of withdrawal signs. A dose of 5 to 20 mg of diazepam can be given intravenously every 5 to 10 minutes until the patient is lightly somnolent, followed by 5 to 20 mg every few hours as needed to control delirium and agitation, with a ceiling dose of about 60 mg of diazepam per day. After the patient is stable for 2 to 3 days, the benzodiazepine can be slowly tapered over 7 to 10 days. In elderly patients or those with liver disease, repeated administration of shorter-acting benzodiazepines such as oxazepam or lorazepam may be safer. A third approach is symptom-guided by monitoring instruments such as the revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar), which is a 10-item scale that can be administered at the bedside within 5 minutes. Using a CIWA-Ar score of at least 8 as a cutoff, treatment begins with diazepam (5 to 10 mg) followed by hourly assessment and repeated dosing until the score is less than 8. Thereafter, assessments can be made every 4 to 8 hours to determine the need for repeated dosing. All treatment methods have similar efficacy, but the loading-dose and the symptom-guided approaches may be faster and use less drug than the repeated fixed-dose method, resulting in less sedation and less risk of respiratory depression.

Patients refractory to benzodiazepines may respond to addition of a different class of sedative-hypnotic (e.g., barbiturates or propofol). Neuroleptics, such as haloperidol, are reserved for severe agitation as adjunctive therapy. Fluid and electrolyte abnormalities can be severe and require prompt therapy. Dehydration accompanying delirium tremens may require replacement of up to 4 to 10 liters of fluid during the first 24 hours. Hypomagnesemia is common, lowers seizure threshold, and should be treated with magnesium sulfate (e.g., 1 g intravenously every 6 hours during the first day in patients with adequate renal function). Potassium should be included in intravenous solutions because hypokalemia may be exacerbated by glucose administration, leading to cardiac arrhythmias.

DISORDERS OF COGNITION

More than 10 percent of patients with alcohol use disorder develop cognitive dysfunction.[3] The pathogenic mechanisms are often multiple and include neurotoxic effects of ethanol, nutritional deficiencies, and electrolyte disturbances. Several alcohol-related clinical syndromes with cognitive dysfunction as a prominent feature have been described.

Alcohol-Related Dementia

People with severe alcohol use disorder can suffer progressive memory impairment along with aphasia, agnosia, apraxia, or impaired executive function that persists beyond periods of intoxication or withdrawal and cannot be attributed to other causes. Heavy alcohol use can result in brain atrophy with neuronal loss in the frontal cortex, hypothalamus, and cerebellum; a reduction in the size of cell bodies and dendritic arbors in layer III pyramidal neurons of the superior frontal gyrus and motor cortices; and white matter loss, particularly in the hippocampus, corpus callosum, and cerebellum.[4] With several years of abstinence, cognitive function can improve.

Brain imaging studies have shown widespread volume loss affecting cortical gray and white matter and signal abnormalities in several subcortical structures, including the corpus callosum, pons, cerebellar hemispheres, and vermis.[5] These regions are less affected in patients with uncomplicated alcohol use disorder free of alcohol-associated electrolyte and nutritional disturbances. White matter abnormalities may be observed with greater sensitivity and detail using diffusion tensor imaging. These imaging and neuropsychiatric abnormalities are partly reversible during abstinence. Volume loss and recovery during abstinence may reflect changes in brain water, but longitudinal studies using MR spectroscopy have shown increases in *N*-acetyl aspartate and phospholipids in certain brain regions, suggesting actual recovery of neurons and white matter during abstinence.

Wernicke Encephalopathy

Wernicke encephalopathy is an acute disorder manifested by the classic triad of nystagmus and ophthalmoplegia, gait ataxia, and an acute confusional state.[6] However because not all patients exhibit the complete triad and because the diagnosis can be difficult to distinguish from drunkenness and other causes of confusion, it is missed in 75 to 80 percent of cases. To avoid underdiagnosis, one should consider Wernicke encephalopathy when two of the following four signs are present: dietary deficiency, oculomotor abnormalities, cerebellar dysfunction, and either an altered mental state or memory impairment. The differential diagnosis includes sedative drug intoxication and structural lesions of the posterior fossa. In the absence of overt ocular signs in patients with confusion or ataxia, the differential diagnosis includes ethanol intoxication and encephalopathy due to other causes such as hepatic insufficiency or infection. Magnetic resonance imaging (MRI) and sensitive measures of serum thiamine can improve diagnostic accuracy but should not delay treatment. The most characteristic MRI findings are of cytotoxic and vasogenic edema involving the thalamus, hypothalamus, and brainstem, appearing as symmetric signal intensities on T2-weighted images of medial thalamic nuclei, periventricular gray matter, midbrain tectum, and the mammillary bodies. Less common are symmetric alterations in the cerebellum, dentate nuclei, cranial nerve nuclei, caudate, splenium of the corpus callosum, and cerebral cortex.

Neuropathologic findings include neuronal loss, demyelination, glial and vascular proliferation, hemorrhage, and necrosis, particularly affecting the anterior and mediodorsal thalamus, mammillary bodies, basal forebrain, raphe nuclei, and cerebellar vermis. An underlying disorder that predisposes to malnutrition appears to be common to all cases. Alcohol use disorder is the most frequent predisposing factor. However, persistent vomiting due to a variety of causes such as starvation, malignancy or other chronic systemic diseases, and other mainly surgical causes of malabsorption has also been implicated,[6] as described in Chapter 13.

The link between malnutrition and Wernicke encephalopathy is a deficiency of vitamin B_1 (thiamine). In people with chronic alcohol use disorder, decreased dietary intake of thiamine may be compounded by alcohol-induced defects in intestinal absorption, metabolism, and hepatic storage of thiamine.[6] Thiamine pyrophosphate is a required cofactor for at least four enzymes involved in intermediary metabolism: pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, transketolase, and branched-chain α-ketoacid dehydrogenase. Metabolic impairment in glucose utilization, impaired amino acid transport and resultant excitotoxicity, impaired ion transport, acidosis from increased lactate production, and mitochondrial dysfunction with resultant oxidative stress and blood–brain barrier disruption have all been implicated in pathogenesis. Variant forms of transketolase and thiamine transport genes could provide a basis for the preferential vulnerability of certain patients to develop Wernicke encephalopathy.

Treatment of Wernicke encephalopathy is by repletion of thiamine. Patients should be hospitalized and receive 200 to 500 mg of thiamine intravenously three times daily for several days until there is no further improvement in signs and symptoms. It is important that thiamine replacement is started prior to or concurrent with administering glucose, to avoid worsening the encephalopathy. Improvement with therapy is considered evidence of correct diagnosis. Acute, reversible MRI abnormalities have also been described, and may be helpful in confirming the diagnosis in mild cases or those with atypical clinical features. Detection of a low blood thiamine level may also be useful; current guidelines recommend that total blood thiamine levels be sent at first diagnosis, immediately before beginning thiamine replacement.

The prognosis of Wernicke encephalopathy depends on the prompt institution of appropriate treatment. The overall mortality rate is about 17 percent.[6] After the institution of treatment, ocular and gaze palsies begin to improve within hours to days, and nystagmus, gait ataxia, and confusion within days to weeks. Long-term sequelae include residual nystagmus or gait ataxia in approximately 60 percent of patients and a chronic memory disorder (Korsakoff amnestic syndrome) in more than 80 percent.

Korsakoff Syndrome

Korsakoff syndrome is characterized by a disproportionate impairment of memory that typically arises in chronic alcoholics in the wake of one or more episodes of Wernicke encephalopathy. The main behavioral deficits are impairment of anterograde episodic memory, with semantic and retrograde memory affected to a lesser extent. The disability afflicting these patients is one of the most striking in clinical neurology. There is an inability to incorporate new memories (anterograde amnesia) and impaired retrieval of previously established, especially recent, memories (retrograde amnesia). Immediate recall is intact. Patients are typically disoriented to time and place, and hospitalized patients are characteristically unaware of their room numbers or hospital floor, how long they have been in the hospital, what they had for their last meal, or who visited them. At the same time, very distant memories may be preserved in detail; some patients appear to be stuck in time, insisting that the year is one from decades past. Patients with Korsakoff syndrome appear to be unaware of their deficit and commonly attempt to reassure the examiner that nothing is seriously wrong. Confabulation, the invention of material to fill in gaps in memory, is often but not invariably seen. Other aspects of cognitive function may exhibit subtle impairment, but alertness and language are intact. Emotional changes such as apathy or mild euphoria may also develop.

The distribution of histopathologic lesions is identical to that seen in Wernicke encephalopathy. Episodic memory processing requires a network of limbic structures, many of which are damaged in Korsakoff syndrome. Biochemical studies have provided evidence of oxidative stress, glutamate-mediated excitotoxicity, and inflammation in vulnerable brain regions as major mechanisms for brain damage due to thiamine deficiency.[7] Patients with Korsakoff syndrome may show evidence of other alcohol-related neurologic disorders. Nystagmus and gait ataxia related to past bouts of Wernicke disease are common, as are signs of a peripheral neuropathy. In many patients there is also evidence of frontal lobe dysfunction. The differential diagnosis of a chronic amnestic syndrome resembling Korsakoff syndrome includes pancerebral hypoxia or ischemia, bilateral posterior cerebral artery strokes, herpes simplex virus encephalitis, paraneoplastic limbic encephalitis, and brain tumors in the vicinity of the third ventricle. Although acute Wernicke encephalopathy should always be treated with thiamine, the effectiveness of thiamine in preventing the subsequent development of the chronic amnestic syndrome is uncertain. Similarly, thiamine has not been shown to be effective for the treatment of established Korsakoff syndrome, although patients with this disorder may improve spontaneously.

Pellagra

Endemic pellagra, which results from deficiency of niacin (vitamin B_3) or its amino acid precursor tryptophan, is an underappreciated cause of confusion and delirium in malnourished alcoholics.[8] Neuropathologic changes are most prominent in neurons of the pons and deep cerebellar nuclei, though neurons elsewhere are also involved. Affected neurons show chromatolysis, appearing swollen and rounded, with eccentric nuclei and loss of Nissl substance. Systemic manifestations of pellagra include diarrhea, glossitis, anemia, and erythematous cutaneous lesions that appear in sun-exposed areas. Although pellagra was named for the characteristic skin lesions, they are not always present. Early mental symptoms of irritability, depression, fatigue, insomnia, and inability to concentrate are nonspecific and suggest a psychiatric disorder. However, the later development of confusion, hallucinations, or paranoid ideation is characteristic of pellagra, and is usually accompanied by spastic weakness and extensor plantar responses. Tremor, rigidity, polyneuropathy, optic neuritis, and deafness may also be present. Pellagra responds readily to administration of niacin, although cerebral symptoms may not be completely reversible. Further details are given in Chapter 15.

Marchiafava–Bignami Disease

Marchiafava–Bignami disease is a rare disorder characterized by destruction of myelin mainly in the corpus callosum and anterior commissure.[9] Exceptionally, lesions extend laterally to involve the centrum semiovale, and in some instances the middle cerebellar peduncles are also demyelinated. Neurons in layer III of the cerebral cortex may be replaced by gliosis, possibly owing to disruption of involved callosal fibers. The disease is usually diagnosed at postmortem examination because the clinical signs are nonspecific, although MRI has made diagnosis more feasible during life. Most patients are alcoholics of long standing and many have associated malnutrition or liver disease, although the disease has appeared in a few nondrinkers. The etiology is not known.

Patients may present acutely with seizures and coma often accompanied by signs of upper motor neuron dysfunction, or alternatively they may follow a subacute course with gait disturbance, dysarthria, hyperreflexia, cognitive impairment, neuropsychiatric symptoms, and signs of interhemispheric disconnection. Cerebrospinal fluid (CSF) demonstrates a normal white blood cell count but may show elevated protein. Brain MRI features T2-hyperintense swelling of the corpus callosum, followed later in the course by callosal atrophy along with cortical and subcortical atrophy. T1-weighted images may show hypointense necrotic lesions of the corpus callosum. There may be gadolinium enhancement of lesions. Motor deficits, such as pyramidal tract signs and gait disturbances, tend to recover with abstinence from alcohol and improved nutrition, but many patients show residual cognitive impairment and a disconnection syndrome. About 10 percent of patients with concomitant alcohol use disorder show a good outcome. Early treatment with thiamine has been associated with a better outcome. People with multiple lesions on MRI are more likely to have a poor outcome. Patients who develop coma carry the greatest risk of serious disability or death, whereas those with little impairment in consciousness may recover with only mild disability.

Hepatocerebral Disorders

Severe alcoholism can cause hepatic cirrhosis with portocaval shunting and hepatic insufficiency, leading to serious secondary neurologic disorders. In its mildest, covert form, hepatic encephalopathy presents with a normal neurologic examination and deficits apparent only on psychometric testing. Overt hepatic encephalopathy presents as a confusional state with deficits in awareness, attention, and calculation ability or, in severe cases, somnolence, stupor, and coma. The pathogenesis and treatment of hepatic encephalopathy are discussed in Chapter 12.

Acquired (non-Wilsonian) hepatocerebral degeneration is a less common disorder that can accompany advanced liver disease and is characterized by parkinsonism, ataxia and, in some patients, dystonia, chorea, and orobuccolingual dyskinesia.[10] Cognitive dysfunction is common but is not always present. Occasional patients show signs of a myelopathy with corticospinal tract signs. Acquired hepatocerebral degeneration begins insidiously after many weeks or years of hepatic dysfunction and is usually progressive, with episodes of stability or spontaneous remissions and relapses. It is characterized by neuropathologic lesions that resemble those found in Wilson disease with diffuse, patchy necrosis and microcavitation at the junction of cerebral gray and white matter, and a loss of neurons and myelinated fibers in the basal ganglia and cerebellum. Protoplasmic type II (Alzheimer) astrocytes are increased in number, and Opalski cells may be present.

Acquired hepatocerebral degeneration is thought to result from central nervous system exposure to neurotoxic substances present in the portal circulation, such as ammonia, aromatic amino acids, and metals. A role for manganese in particular is supported by elevated serum and CSF manganese levels and by pallidal hyperintensities on T1-weighted MRI images of patients with severe liver disease, reminiscent of findings in occupational manganese toxicity. Dopaminergic drugs may reduce parkinsonian symptoms, although less effectively than in patients with Parkinson disease. Death usually occurs as a complication of advanced liver disease or intercurrent infection.

ALCOHOLIC CEREBELLAR DEGENERATION

In several alcoholic patients, a chronic cerebellar syndrome develops, sometimes as a long-term sequela of Wernicke encephalopathy. The neuropathologic features of alcoholic cerebellar degeneration include loss of cerebellar cortical neurons, especially Purkinje cells, with a particular predilection for the anterior and superior vermis; the anterior and superior cerebellar hemispheres are affected less often.[11] The distribution of this cerebellar pathologic process is strikingly similar to that seen in Wernicke encephalopathy, suggesting that the two disorders are linked pathophysiologically. Alcoholic cerebellar degeneration may also result from a direct toxic effect of alcohol on the cerebellum, or from a combination of thiamine deficiency and alcohol neurotoxicity.

The natural history of alcoholic cerebellar degeneration is variable. The syndrome usually occurs in the setting of chronic alcoholism of 10 years or more duration. The most frequent mode of onset is with ataxia that progresses steadily for weeks to months. A more gradually progressive disorder that evolves over years is also common. Less often, a mild and stable chronic deficit may suddenly worsen.

Although gait ataxia is the most prominent manifestation of both alcoholic cerebellar degeneration and Wernicke encephalopathy, the pattern of involvement in the two disorders may differ. Limb ataxia, which is absent in most patients with Wernicke encephalopathy, is usually detectable in alcoholic cerebellar degeneration. Examination of such patients typically demonstrates severe ataxia of the legs, with milder involvement of the arms. Dysarthria, which is usually mild, is also more frequent in alcoholic cerebellar degeneration than Wernicke encephalopathy. In contrast, nystagmus is present less often than in Wernicke encephalopathy. Patients with alcoholic cerebellar degeneration may also exhibit signs of a polyneuropathy (see later). Uncommon manifestations of alcoholic cerebellar degeneration include hypotonia, ocular dysmetria, and postural tremor.

Alcoholic cerebellar degeneration is a clinical diagnosis. Neuroimaging may show cerebellar cortical atrophy, but laboratory findings usually are helpful only for excluding other causes of ataxia. Other conditions that must be considered in the differential diagnosis of subacute or chronic cerebellar ataxia in middle life include multiple sclerosis, hypothyroidism, paraneoplastic cerebellar degeneration, idiopathic cerebellar or olivopontocerebellar degeneration, Creutzfeldt–Jakob disease, and posterior fossa tumors. Like alcoholic cerebellar degeneration, many of these disorders can produce ataxia that preferentially affects gait.

Ataxia due to alcoholic cerebellar degeneration often stabilizes or improves with cessation of drinking and improved nutritional status, although the relative importance of each of these two factors is uncertain. Patients should receive parenteral thiamine, although it is not yet known whether thiamine improves outcome, as it does in Wernicke encephalopathy.

CENTRAL PONTINE AND EXTRAPONTINE MYELINOLYSIS

Central pontine and extrapontine myelinolysis are forms of the osmotic dysregulation syndrome which is further discussed in Chapter 17. Patients typically present with seizures or confusion that improves but then is followed by rapidly evolving dysarthria, dysphagia, oculomotor dysfunction, and paraparesis or quadriparesis. A history of alcohol use disorder is common and found in 58 percent of affected patients.[12] Malnutrition accounts for 17 percent and nonalcoholic cirrhosis for 12 percent of cases. Less often, it develops with burns, renal failure, prolonged use of diuretics, psychogenic polydipsia, or pituitary or urologic surgery.

The characteristic pathologic lesion in central pontine myelinolysis is bilaterally symmetric, focal destruction of myelin in the ventral pons. Histologically, there is severe loss of myelin, and oligodendroglia are reduced in number. Neurons and axons are relatively spared, although axonal swelling and neuronal shrinkage may occur, particularly in the center of lesions. There is no inflammation, and blood vessels appear normal. In approximately 50 percent of cases, characteristic lesions are present outside the basis pontis, and in half of these cases with extrapontine lesions, no pontine lesions are present. Extrapontine myelinolysis has been observed in the cerebellum, thalamus (especially the lateral geniculate body), external and extreme capsules, basal ganglia, deep layers of cerebral cortex and adjacent white matter, and rarely in the fornix, anterior commissure, subthalamic nucleus, amygdala, optic tract, and spinal cord.

Co-existent illnesses often influence the clinical manifestations of central pontine myelinolysis, making it difficult to diagnose in some cases. Although some small lesions detected postmortem can be asymptomatic, certain clinical features are typical. Central pontine myelinolysis often evolves over several days to weeks in a severely ill patient, and mental confusion is a prominent feature in almost all cases. Demyelination of pontine corticobulbar fibers leads to early dysarthria or mutism. Spastic quadriparesis and pseudobulbar palsy are common, occurring in more than 90 percent of patients. When lesions extend into the midbrain, medulla, or pontine tegmentum, there may be pupillary and oculomotor signs, depressed consciousness or coma, and dysfunction of cranial nerves. Progressive demyelination of corticospinal and corticobulbar tracts in the basis pontis may produce a locked-in syndrome. Extrapontine lesions may cause ataxia, parkinsonism, choreoathetosis, and dystonia. Cognitive and behavioral symptoms include restlessness, emotional lability, apathy, agitation, insomnia, paranoia, delusions, rage, and disinhibition.

MRI scans may be normal during the first 2 weeks of illness, but eventually affected regions appear hyperintense on T2-weighted sequences and hypointense on corresponding T1-weighted sequences. Diffusion-weighted MRI may be more sensitive and show lesions within the first few days after onset of symptoms, prior to abnormalities developing on T2-weighted sequences.

Although the disorder has historically been considered to carry a poor prognosis, as many as 50 percent of patients show improvement after several weeks and some otherwise normal-appearing patients have the characteristic MRI abnormalities found incidentally. In general, outcome does not correlate with the severity of neurologic deficits during the acute phase of illness or with the degree of hyponatremia. Therefore, all patients with suspected central pontine myelinolysis should be supported aggressively, especially since substantial improvement may occur after several weeks to months.

Central pontine myelinolysis is mainly an iatrogenic disorder, and its appearance coincided with the widespread use of intravenous therapy for correction of fluid and electrolyte disorders. Hyponatremia frequently precedes central pontine myelinolysis, and aggressive correction of hyponatremia appears to be the precipitating factor in most cases. Over the past 20 years there has developed a consensus on the treatment of hyponatremia to minimize the risk of myelinolysis. Severe hyponatremia (≤ 120 mEq/L), if it develops rapidly, can cause life-threatening symptoms such as coma and seizures, and demands prompt treatment. If hyponatremia occurs slowly, however, symptoms are generally less severe and include malaise, nausea, headache, lethargy, and confusion. The general consensus is to increase the serum sodium level by no more than 12 mEq/L in 24 hours in patients with chronic hyponatremia.

ALCOHOL-RELATED NEUROPATHY

Neuropathy is the most frequently encountered chronic neurologic disorder related to alcohol abuse.[13] Both nutritional deficiency and a direct, toxic, dose-dependent effect of alcohol have been invoked as etiologies. Support for a toxic effect of ethanol comes from studies in rats demonstrating hyperalgesia following several weeks of ethanol ingestion. Axonal degeneration appears to be the principal pathogenic process. Segmental demyelination also occurs and may be secondary to the primary axonal disorder or a consequence of concomitant nutritional deficiency.

Alcoholic neuropathy usually presents after several years of alcohol abuse as a distal, symmetric, sensorimotor polyneuropathy that is gradual in onset and slowly progressive. Symptoms include weakness, pain, paresthesia, muscle cramps, numbness, gait ataxia, and burning dysesthesia. Neurologic examination may reveal any combination of reflex, sensory, and motor abnormalities, with predominant involvement of the legs. Absent or decreased muscle stretch reflexes and impaired vibration sense in the lower extremities are virtually universal findings. Defective appreciation of light touch and weakness are also seen in most patients. Pain and temperature sensation are affected less often, and symptomatic autonomic dysfunction and cranial nerve involvement are comparatively rare. In addition to the neurologic abnormalities, affected limbs may exhibit edema, hyperpigmentation or ulceration of the skin, and bony deformities.

Nerve conduction studies are useful for documenting the presence of neuropathy and for demonstrating the predominantly axonal pathologic process. Laboratory studies on blood and CSF can exclude other causes of polyneuropathy including diabetes, chronic inflammatory demyelinating polyneuropathy, uremia, dysproteinemia, and vasculitis.

Vitamin supplementation (especially thiamine) and abstinence from alcohol can often arrest the progression of alcoholic polyneuropathy and in some cases lead to clinical improvement. Neuropathic pain may respond to anticonvulsants or tricyclic antidepressants.

ALCOHOL-RELATED MYOPATHY

Excessive alcohol consumption has adverse effects on both skeletal and cardiac muscle. Both acute and chronic clinical presentations of alcohol-related myopathy are recognized.

Acute Necrotizing Myopathy

An acute, necrotizing myopathy may develop over the course of 1 to 2 days in the setting of heavy binge drinking and affects up to 2 percent of heavy drinkers. Symptoms include muscle pain and weakness, which, although classically symmetric and proximal in distribution, may be asymmetric or focal in nature. Neurologic examination shows tender, swollen muscles in the affected areas. Weakness is a prominent finding and may be associated with dysphagia. Signs of congestive heart failure are sometimes present.

Laboratory abnormalities include moderate to severe elevation of serum creatine kinase levels, and in some cases myoglobinuria. The electrocardiogram may reveal arrhythmias or conduction defects. Electromyography discloses myopathic changes in configuration and recruitment of motor unit potentials, as well as fibrillation potentials. The muscle biopsy shows necrosis of muscle fibers.

Acute alcoholic myopathy must be distinguished from other causes of acute weakness in alcoholic patients, such as hypokalemia and hypophosphatemia. In hypokalemia, weakness is not accompanied by muscle pain, and myoglobinuria does not occur. Hypophosphatemia closely reproduces the clinical features of acute alcoholic myopathy and may also contribute to its pathogenesis. Consequently, serum potassium and phosphorus concentrations should always be measured in acutely weak alcoholic patients.

Complications of acute alcoholic myopathy, such as cardiac disturbances and renal compromise due to myoglobinuria, should be treated urgently. Electrolyte abnormalities should be monitored carefully and corrected if necessary. Muscle pain and tenderness may improve with analgesics. With abstinence, recovery within weeks to months is the rule, but some patients exhibit residual weakness and long-standing cardiac conduction abnormalities.

Chronic Myopathy

The much more common form of alcohol-related myopathy is a chronic condition which develops insidiously over weeks to months, and is seen in 40 to 60 percent of patients, typically those with a history of more than 10 years of heavy alcohol use.[14] In animal and cell-culture studies, alcohol reversibly inhibits initiation of translation and protein synthesis in skeletal muscle.

In addition, disruption of carbohydrate and energy metabolism, oxidative stress, and apoptosis appear to contribute to myopathy. Chronic alcoholic myopathy is characterized by proximal weakness involving pelvic and shoulder girdles, with relative preservation of muscle stretch reflexes. In contrast to acute necrotizing alcoholic myopathy, muscle pain is uncommon or mild. Patients often show signs of other ethanol-induced end-organ damage such as cirrhosis or cardiomyopathy. Serum creatine kinase levels are elevated three- to sixfold in 40 percent of patients. When the clinical diagnosis is uncertain, chronic alcoholic myopathy can be distinguished from polyneuropathy by electrodiagnostic studies or by muscle biopsy, which shows atrophy mainly of type II muscle fibers along with myocyte necrosis without inflammation. The chronic form of myopathy is related to lifetime alcohol dose and may improve with abstinence or decreased drinking.

ALCOHOL AND STROKE

Epidemiologic studies suggest that alcohol consumption influences the risk of stroke.[15] For intracerebral and subarachnoid hemorrhage, the risk increases linearly with increasing daily alcohol intake. Possible explanations for this association include alcohol-induced disorders of coagulation or fibrinolysis, thrombocytopenia or impaired platelet function, and acute or chronic hypertension. In contrast, the relationship between daily alcohol intake and ischemic stroke is J-shaped. Thus, moderate drinking—two or fewer drinks per day—appears to reduce ischemic stroke risk compared with that observed in nondrinkers, whereas less temperate drinking patterns predispose to ischemic stroke. The protective effect of small amounts of alcohol has been attributed to elevated levels of prostacyclin, decreased platelet activation, enhanced fibrinolysis, increased levels of high-density lipoprotein cholesterol, and activation of signaling mechanisms involved in ischemic preconditioning. Mechanisms that could be responsible for an increased risk of ischemic stroke in heavy drinkers include alcohol-related cardiomyopathy or arrhythmias, alcohol-induced hypertension, the increased incidence of cigarette smoking in heavy drinkers, rebound thrombocytosis occurring with alcohol withdrawal, and hypercoagulable states.

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CHAPTER

34

Neurologic Complications of Recreational Drugs

S. ANDREW JOSEPHSON

COCAINE
METHAMPHETAMINES
BATH SALTS AND FLAKKA
MDMA (ECSTASY)
GAMMA HYDROXYBUTYRATE
SEDATIVE-HYPNOTICS
OPIATES
HALLUCINOGENS
N-METHYL-D-ASPARTATE ANTAGONISTS
DEXTROMETHORPHAN
NITROUS OXIDE
MARIJUANA AND RELATED COMPOUNDS
INFECTIOUS COMPLICATIONS OF INJECTION DRUG USE
CONCLUDING COMMENTS

Recreational drug use can lead to neurologic problems stemming from both acute intoxication and chronic use, and physicians must be aware of these complications when faced with any patient presenting with neurologic symptoms. The landscape of drug use has shifted from primarily illicit substances manufactured with the sole purpose of recreational drug use, to the realization that many drugs of abuse are prescription medications. No longer do abusers need to obtain drugs exclusively on the street; physician offices, pharmacies, and medicine cabinets now have become common sources of these substances. Practitioners need to be aware of the potential for abuse by patients when prescribing these substances and also of the potential for these drugs to fall into the hands of other users, including family members and acquaintances of patients. This shift to abuse of prescription drugs has also changed the demographics of those at risk of drug abuse; young and old alike, spanning the full array of socioeconomic backgrounds, are at risk of abuse in the setting of relatively easy accessibility of these substances.

Standard urinary drug screens are inexpensive and utilized in most emergency departments when concern exists for acute intoxication. These screens also are employed in drug treatment programs and employee screens in order to monitor compliance with abstinence. They test for commonly used recreational drugs or their metabolites including alcohol, amphetamines, barbiturates, benzodiazepines, cannabis, and cocaine. Although this list captures many drugs of abuse, many agents discussed here are not included in typical urinary screens and either cannot be tested for easily or are only detected using serum screens that tend to be expensive and time-consuming. These serum screens remain the gold standard for testing, especially outside of the emergency setting. Other options for testing employed much less commonly include saliva and hair analysis, the latter having the advantage of detecting some drugs of abuse weeks to even months after ingestion.

COCAINE

Cocaine is a widely used, highly addictive stimulant that increases monoamine neurotransmitters through inhibition of reuptake. It is taken in a variety of different ways including by snorting, smoking (often as “crack” cocaine), and intravenous injection. Acute intoxication effects and risk depend on the method of ingestion and dose but, in general, as with other stimulants, a variety of neuropsychiatric effects—including psychosis and paranoia—can occur in addition to the expected euphoria and increased energy.

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Adverse neurologic effects may include tremor and a number of other movement disorders including acute dystonia, tics, and dyskinesias, the latter of which can be long-lasting in some patients. As with other stimulant drugs, seizures can occur with acute intoxication and are difficult to predict by dose or route of drug administration; generalized tonic-clonic seizures are most common, but cocaine lowers the seizure threshold and can lead to focal-onset seizures in patients with an underlying brain lesion. Thus, any focality to seizures occurring in the setting of cocaine use should lead to urgent neuroimaging to exclude an underlying structural cause.

The most recognizable of the acute neurologic complications associated with cocaine are cerebrovascular in nature.[1] Dramatic rises in blood pressure shortly after use can lead to intracerebral hemorrhage as a result of exceeding the upper limits of the cerebral autoregulatory curve. In addition, patients with intracranial aneurysms may be at risk of rupture with the hypertension that accompanies intoxication. Ischemic stroke can also occur shortly after use due to the promotion of thrombosis via platelet activation and other downstream mechanisms; this hypercoagulability was first described in myocardial infarction but applies similarly to ischemic stroke.

In contrast to the acute effects, chronic cocaine use can lead to ischemic stroke and cerebral transient ischemic attacks (TIAs) through a variety of mechanisms, many of which remain incompletely understood. Some cocaine abusers appear to develop a noninflammatory vasculopathy similar to accelerated atherosclerosis in both large and small vessels of the intracranial circulation, predisposing them to stroke at a young age. It has been suggested that part of the rise in stroke incidence in younger populations is accounted for by the increased use of recreational stimulants such as cocaine.[2] Other purported mechanisms of cocaine-induced stroke have included vasospasm of small arteries and an increased incidence of cervical artery dissection—these appear to be less common than atherosclerotic-like changes but should be considered in cocaine-related stroke and TIAs.

In addition to direct effects on the cerebral circulation, a variety of ischemic cocaine-related complications stem from the varied effects of the drug on the heart. Cocaine-induced arrhythmias, both atrial and ventricular, can predispose to cardioembolic events with either acute or chronic use of the drug. The cardiomyopathy that accompanies cocaine-related myocarditis can also lead to cardioembolic disease when the ejection fraction is moderately-to-severely depressed. Myocardial infarction in the setting of acute use is one of the more common causes of concern when a cocaine user presents to the emergency department with chest pain. Stroke can occur when wall motion abnormalities of the heart or an apical aneurysm set the stage for stasis and intracardiac clot formation that can subsequently embolize to the cerebral circulation. Acute aortic dissection, which is well described in cocaine users due to effects on the aortic endothelium and to acute hypertension, can lead to cerebrovascular events when the dissection involves the origins of the great vessels, leading to either hypoperfusion or a proximal embolic source.

Acute and chronic white matter changes have also been described with cocaine use. Chronic changes likely reflect in part the effects of sustained hypertensive episodes and may present with cognitive decline featuring prominent executive dysfunction. A more fulminant acute leukoencephalopathy may in some cases be due to adulterants found in cocaine, including the antiparasitic medication levamisole.

METHAMPHETAMINES

The numerous methamphetamine-containing compounds that are available to recreational users all work through a common mechanism of increased norepinephrine, epinephrine, and serotonin transmission at the synapse while also activating dopamine receptors. The stimulant effects of acute intoxication are therefore similar in many respects to those occurring with cocaine, with euphoria and increased energy predominating along with the risk of occasional paradoxical reactions including agitation and paranoia. As the effects of the drug wear off, dysphoria and increased sleep commonly occur, mimicking some of the effects of sedatives.

Other neurologic effects of acute intoxication involve intracerebral hemorrhage due presumably in part to severe hypertension, even in patients without a history of chronic use; subcortical locations of hemorrhage are most common. As with other stimulants, tremor and tonic-clonic seizures can occur with acute intoxication. Any focal features of the seizure or in the postictal period should trigger a neuroimaging search for an underlying lesion.

A number of neuropsychatric complications are well described in chronic users of methamphetamines. Psychosis, attention-deficit hyperactivity disorder, and

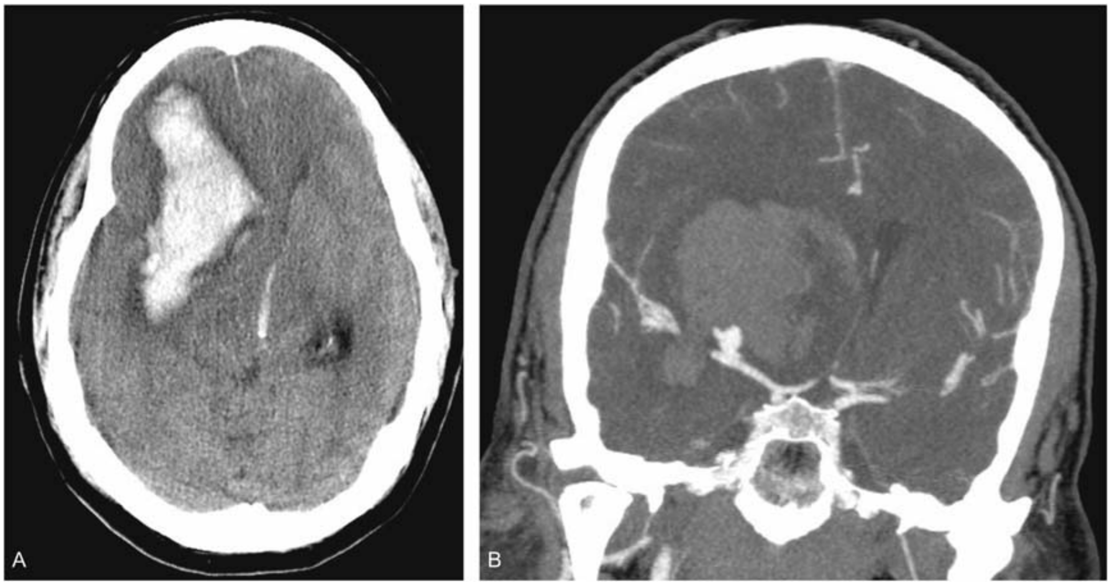

FIGURE 34-1 ■ Noncontrast CT (*A*) and CT angiogram (*B*) of the brain in a 41-year-old man with a history of chronic methamphetamine abuse who presented with confusion and left hemiparesis. A large right-hemispheric intracerebral hemorrhage is demonstrated, resulting from a bilobed 8 × 8 × 6-mm aneurysm in the region of the right middle cerebral artery bifurcation.

chronic memory and executive function deficits may occur, with resultant-poor psychosocial and behavioral outcomes. Individuals who chronically abuse methamphetamines typically require psychologic assistance in addition to substance abuse counseling. The chronic neurotoxicity that leads to these complications is thought to involve both dopaminergic and serotonergic fronto-striatal-thalamocortical networks. Compulsive performance of repetitive, mechanical tasks such as assembling or disassembling an object, termed "punding," is likely the result of this dopaminergic overactivity and is well described in chronic users of methamphetamines (termed "tweaking" by some users).[3] Although studies have been mixed, users of methamphetamines may have an increased risk of developing parkinsonism later in life due to involvement of striatal dopamine pathways; additional longitudinal investigations are addressing this possibility.

Cerebrovascular complications of chronic methamphetamine use include the development of an often dramatic cerebral vasculopathy with fusiform enlargement of the large vessels of the brain with a tendency toward aneurysm formation (Fig. 34-1). These aneurysms can be large enough to contain clot, which serves as an embolic source for ischemic stroke. Other patients with vasculopathy in the setting of methamphetamine use demonstrate narrowing of some distal branches of the cerebral vessels, leading to ischemia.[4] It is likely that this vasculopathy is a result, at least in part, of direct toxicity of the drug or adulterants rather than simply the consequence of hypertension. Some have suggested an inflammatory process (e.g., cerebral vasculitis) within the vessel wall, although studies supporting this have been mixed, and typical findings in the cerebrospinal fluid and on histologic and gross pathologic examination are noninflammatory.

In addition to an increased risk of ischemic stroke, methamphetamine abusers have an increased risk of subarachnoid hemorrhage relating to their tendency to aneurysm formation. In patients with methamphetamine-related subarachnoid hemorrhage, the complications of vasospasm and delayed cerebral ischemia are particularly common and severe, even when adjusted for severity of bleed. These effects are apparently more long-lasting than in most patients with aneurysmal subarachnoid hemorrhage and require vigilance for 3 to 4 weeks following initial bleed. As a result, subarachnoid hemorrhage has a worse prognosis when related to methamphetamine use than otherwise, when adjusted for Hunt and Hess grade. Similar to cocaine, methamphetamines can also importantly lead to a cardiomyopathy, myocardial ischemia, or aortic dissection, all of which predispose patients to stroke.

BATH SALTS AND FLAKKA

An increase of the use of so-called bath salts has been recently observed, particularly in the United

States. These compounds, which contain various synthetic cathinones and have no relationship with actual substances used in bathing, are usually swallowed or snorted with effects similar to other stimulants.[5] The mechanism of action involves interactions with plasma membrane transporters for dopamine, norepinephrine, and serotonin; the duration of action is typically 3 to 4 hours. Low doses often produce euphoria and increased alertness, but neurologic side effects include tremors and seizures as well as hallucinations, agitation, and dysphoria among some users. An agitated delirium can result that is often accompanied by tachycardia and hyperthermia; this constellation of findings should alert healthcare workers to possible ingestion of these substances, which are not detected by typical drug screens. These compounds were until recently widely available legally in over-the-counter form. A related synthetic compound, "flakka", was previously legally available and has led to outbreaks beginning in 2014 of a striking hyperactive delirium and rhabdomyolysis; combining this so-called zombie drug with other sedatives and amphetamines is common, especially among young persons.

MDMA (ECSTASY)

The synthetic compound 3,4-methylenedioxymethamphetamine (MDMA, ecstasy, "Molly") is a serotonergic amphetamine that became popular at dance parties ("raves") and is often taken in combination with other psychotropic drugs. As with other stimulants, the desired effects among users are euphoria and a sense of well-being. Ecstasy is also known for leading to disinhibition and sexual arousal. In some patients, agitation and anxiety can paradoxically occur at the time of intoxication or once the acute effects of the drug have worn off.

The association between severe hyponatremia and MDMA ingestion is important to recognize and can lead to serious neurologic complications. Users of the drug develop both a primary polydipsia and a drug-induced increase in antidiuretic hormone secretion, limiting the ability of the kidneys to secrete water and leading to, at times, a precipitous decline in the serum sodium level. The polydipsia may be in part due to an attempt among users to avoid hyperthermia in crowded dance arenas. The resultant hyponatremia may lead to seizures as well as potentially fatal cerebral edema; therefore, serum sodium measurement is important in any patient presenting with altered mental status or seizures following MDMA use. Careful correction is important to avoid osmotic demyelination, as discussed in Chapter 17, although in the setting of life-threatening neurologic complications, more rapid correction may be necessary. As is the case with most stimulants, seizures can also occur with MDMA ingestion independent of the serum sodium level.

Use of MDMA can also lead to a serotonin syndrome characterized by altered mental status, fever, and other neurologic abnormalities such as clonus, myoclonus, and tremor. There is likely a spectrum of this disorder ranging from mild confusion to life-threatening circulatory collapse when autonomic instability occurs. The risk of serotonin syndrome increases when MDMA is combined with other serotonergic drugs such as selective serotonin reuptake inhibitors. Treatment options include supportive care in a cool environment for milder cases to treatment with cyproheptadine in more severe instances.

Individuals with a history of heavy use of MDMA appear to demonstrate cognitive problems in memory and attentional domains that may be long-lasting.[6] Some studies, however, have suggested that these cognitive deficits may relate, at least in part, to underlying comorbidities, including the behavioral and psychologic disturbances that led originally to use of recreational drugs. These chronic cognitive effects seem to be mainly observed in those with a history of heavy use rather than in those with more infrequent use of the drug.

GAMMA HYDROXYBUTYRATE

Gamma hydroxybutyrate (GHB) leads to both euphoria and stimulant effects with purported sexual enhancement and disinhibition. The drug is the precursor to γ-aminobutyric acid (GABA), one of the most common inhibitory neurotransmitters in the central nervous system. Previously marketed for body-building, it is now used recreationally, often simultaneously with other "club drugs" including MDMA. The drug is ingested orally, usually in liquid form. GHB has a narrow window of safety and therefore overdosing and emergency department visits are common.[7] Interestingly, the drug has found a therapeutic purpose and is marketed for treatment of narcolepsy with cataplexy or excessive daytime sleepiness.

The most commonly cited neurologic effect of GHB intoxication is coma, which may occur rapidly after ingestion and necessitate intubation and admission to the hospital in order to protect the airway and avoid fatal ventilatory failure. Since GHB is not detected in most routine urine toxicology screens, neurologists are often consulted for an otherwise unexplained coma in a young person. An impressively sudden reversal of coma is sometimes observed, which is strongly suggestive of GHB intoxication. Other neurologic complications of acute use include ataxia and nystagmus. Its effects on consciousness may preclude safe driving.

When GHB wears off, an agitated delirium with self-injurious behavior may be observed, and some patients will alternate quickly between agitated and sedated states. Patients with GHB intoxication are at risk of seizures, and myoclonus is typically seen especially when patients are in the agitated phase. Patients using GHB are usually quite amnestic to events, even when they are conscious, leading to its use in sexual assault.

SEDATIVE-HYPNOTICS

The sedative-hypnotic class of drugs is mainly used for medical purposes including induction of sleep and relief of anxiety. However, these compounds have developed into common drugs of abuse with a potential for dependence as prescription drug abuse has increased. Historically, barbiturates were replaced by the benzodiazepine class of drugs in part due to an increased safety profile in overdose; however, both classes of drug have a similar potential for abuse. The sedative and anxiolytic properties of all of these medications resemble those of alcohol since both act in part at the level of the GABA system in the brain; alcohol withdrawal syndromes are treated with long-acting forms of these drugs.

The sedation that accompanies acute intoxication represents an important neurologic manifestation of these compounds that is typically easy to recognize. Reversal of acute intoxication with benzodiazepines by flumazenil, a benzodiazepine receptor antagonist, for purely diagnostic purposes is generally discouraged, and its use is limited to life-threatening situations, given its tendency to produce seizures and rapidly induce withdrawal.

The most important neurologic effects of sedative medications involve withdrawal, which can lead to tachycardia, agitation, tremor, and hallucinations that may develop into frank psychosis. Seizures are an important concern, and abrupt withdrawal of these medications can lead to ictal events even in those without an underlying epileptic disorder. Treatment for these seizures usually involves administration of benzodiazepines, often in intravenous form, followed by a slow taper which may need to last for days or weeks depending on the duration and dose of use prior to withdrawal. As a general rule, traditional antiepileptic medications that are not of the benzodiazepine or barbiturate class are ineffective.

Recently, a number of benzodiazepine-related substances including zolpidem, zaleplon, and eszopiclone have emerged with a safety profile that is so favorable that they are available in many countries without a prescription for use as a short-term sleeping aid. With this greater availability has emerged a potential for abuse as well as symptoms of withdrawal with prolonged exposure. Some patients may inadvertently use these medications at doses or frequencies that have potentially dangerous effects.[8] Zolpidem in particular has also been widely used by teenagers in the United States to produce a high rather than induction of sleep. Neurologic symptoms that have been described include depression, behavioral changes including irritability, unusual complex behaviors similar to sleepwalking, and severe amnesia for events, leading it to be used by sexual predators.

OPIATES

Abuse of opiates remains an extremely important public health concern. Emphasis has shifted from abuse of intravenous heroin and similar substances to recreational use of opiates prescribed for pain relief.[9] Physicians need to be particularly aware of this possibility when prescribing these medications—many of these drugs end up either for sale on the street or abused by persons other than the individual for whom the prescription was intended.

The neurologic effects of opiate intoxication are well known and include miosis and an altered mental status that can progress to coma with high doses, especially in those without previous exposure to this class of medications. Some specific opiates can lead to seizures, including fentanyl, meperidine (particularly in the setting of renal insufficiency), tramadol, and pentazocine. Individuals taking opiates reliably demonstrate diffuse myoclonus, which can be mistaken for seizures or a separate movement disorder, often leading to neurologic

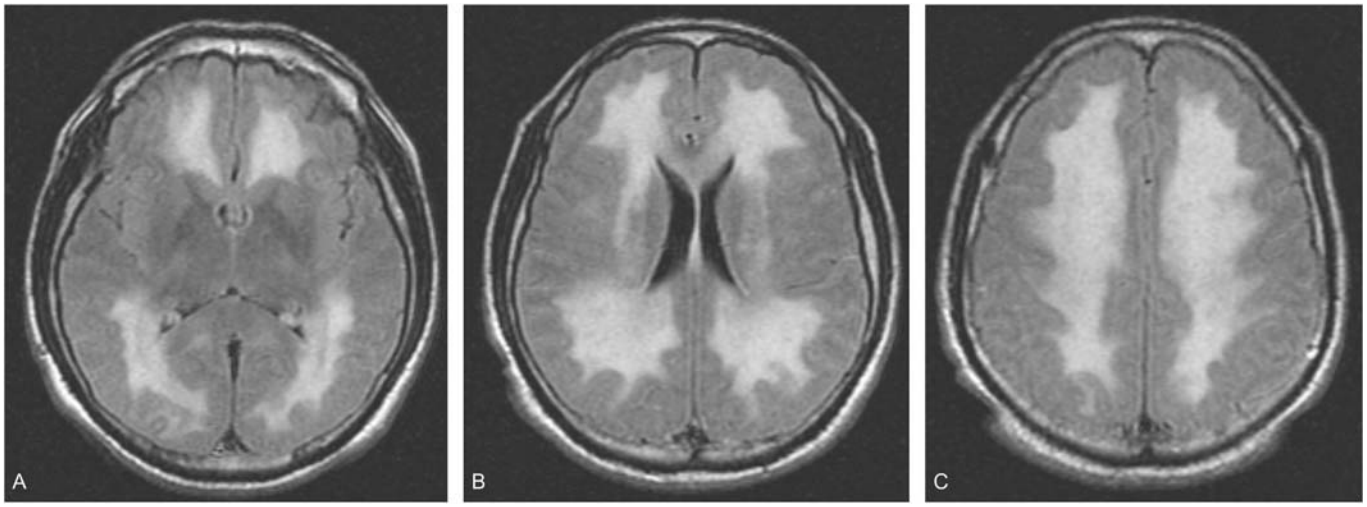

FIGURE 34-2 ■ Axial FLAIR MRI images of the brain from a 39-year-old man presenting with progressive altered mental status and parkinsonism 7 days after inhalation of vaporized heroin ("chasing the dragon"). Extensive white matter hyperintensities spare the subcortical U-fibers. No enhancement occurred on postcontrast images (not shown).

consultation; this condition is generally self-limited and of no consequence, reversing with discontinuation of the drug. Patients in whom opiate intoxication has led to profound respiratory depression are at risk of hypoxic-ischemic injury to the brain and may present with persistent coma even after withdrawal or reversal of opiates. Changes on neuroimaging may be nonexistent or subtle in cases of hypoxic-ischemic injury, and therefore the condition is a diagnosis of exclusion.

There are a number of neuromuscular complications of which opiate abusers are at risk. Myalgias can represent direct muscle involvement from opiate intoxication; frank rhabdomyolysis remains a rare but important complication that needs to be treated aggressively in order to prevent acute kidney injury. Repeated intramuscular injections of opiates may lead to a fibrotic myopathy due to a local direct toxic effect, and therefore users who inject opiates should be asked regarding site of injection.

Beginning in the mid-1990s, an epidemic of wound botulism was described, mainly in California, in users of so-called black tar heroin when the drug was administered via skin popping. This important public health concern can present with outbreaks of multiple cases of botulism in a single community when a batch of the substance becomes contaminated with *Clostridium botulinum*. Patients present with weakness and depressed muscle stretch reflexes, often along with bulbar signs that include difficulty swallowing, double vision, and slurred speech from facial weakness. The pupils may be dilated and poorly reactive to light, but this varies with the serotype of the offending organism and therefore should not be used to make or exclude the diagnosis. If botulism is recognized at an early stage, antitoxin administration is important to avoid ventilatory failure from neuromuscular weakness, which in many cases may be prolonged and necessitate tracheostomy.

Withdrawal from opiate medications reliably leads to dysphoria and akathisia. Muscle pain, nausea, vomiting, yawning, and rhinorrhea are a few of the non-neurologic symptoms of withdrawal that are well recognized. Treatment of life-threatening acute intoxication involves administration of opiate antagonists such as naloxone, which increasingly is widely available to the public in many communities to combat a rise in fatal overdoses. Complications from withdrawal symptoms should be anticipated when these antagonists are given, especially in patients who are chronic users or in whom use involves longer-acting opiate preparations.

When an opiate, often heroin, is inhaled by the user after vaporization on a piece of aluminum foil ("chasing the dragon"), a toxic leukoencephalopathy may result and is characterized on magnetic resonance imaging (MRI) by diffuse and symmetric T2 hyperintensities in the white matter (Fig. 34-2).[10] Symptoms range from mild abulia and parkinsonism to akinetic mutism or coma. Onset of the disorder may be delayed by days to weeks following opiate exposure, and clinical and neuroimaging features may progress before reaching a plateau after a few weeks. There is no effective treatment. Postmortem examination reveals a spongiform-like degeneration in the white matter that spares the U-fibers.

An important, mainly historical, opiate compound is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which in the early 1980s was found to cause a parkinsonian syndrome when the drug was inadvertently created in an attempt to create a synthetic form of meperidine. MPTP leads to neuronal death over a fairly short period of time in neurons in the substantia nigra pars compacta and has led to the development of an important animal model of Parkinson disease.

HALLUCINOGENS

The intent of use of hallucinogens is to alter neurologic perception and mood, often leading to vivid visual illusions which may be colorful and well formed. A distortion of sensory input and synesthesia occurs with the prototypic drug lysergic acid diethylamide (LSD). At times, LSD ingestion can be characterized paradoxically by agitation, panic, or dysphoria in what is termed a “bad trip” by users. Rare adverse effects that may be due to LSD or its adulterants include more permanent visual disturbances and vasospasm leading to cerebral ischemia. Due to its effects on the serotonin receptors in the brain, serotonin syndrome can result, especially when LSD is combined with other serotonergic drugs including prescription antidepressants.

Long-term effects of LSD use may include “flashbacks,” where a hallucination that accompanied intoxication is experienced again months to years later and is usually not distressing. Exposure to serotonergic drugs may be the trigger for such flashbacks in some patients. In contrast, hallucinogen persisting perception disorder is a long-term and potentially disabling recurrent condition in which hallucinations are experienced again; the disorder is unpleasant, disruptive, and difficult to treat.[11]

Other important drugs of abuse with properties similar to LSD include mescaline, which is found in the peyote cactus in the southwestern United States. Ingestion leads to tachycardia, agitation, and mydriasis along with hallucinations and altered perceptions. Mushroom intoxication recreationally involves those that contain psilocybin and are consumed often in dried form; headache often accompanies intoxication with these so-called magic mushrooms.

N-METHYL-D-ASPARTATE ANTAGONISTS

Phencyclidine (PCP, “angel dust”) was first developed as a surgical anesthetic, but some patients developed a long-lasting psychotic syndrome following its administration. The drug subsequently emerged as a recreational drug of abuse due to its dissociative effects. One important site of action for PCP is antagonism of *N*-methyl-D-aspartate (NMDA) glutamate receptors, which are widely distributed in the brain, especially in the medial temporal lobes and throughout the limbic system.

Manifestations of PCP intoxication in the emergency setting include tachycardia, hypertension, violent outbursts, and nystagmus, which classically can be vertical in direction. Higher doses of PCP may induce an acute psychosis with hallucinations and agitation, whereas a striking akinetic mutism with unresponsiveness and preserved eye opening may accompany overdose. PCP’s stimulant effects can lead to hyperreflexia as well as dystonia and occasionally seizures. The agitation that results may itself cause rhabdomyolysis, which has otherwise been attributed to a direct toxic effect of the drug. Long-term use of PCP can lead to a condition resembling chronic schizophrenia, and the drug has been used to create animal models of schizophrenia for research purposes.

The anesthetic ketamine has also emerged as a recreational drug of abuse, sometimes in those prescribed the medication for chronic pain. The main mechanism of action involves NMDA antagonism similar to PCP. One of the advantages of its use in anesthetic settings is its relatively favorable safety profile in high doses and, similarly, respiratory depression is an extremely rare occurrence in abusers. Intoxication is characterized by acute CNS depressant effects of slurred speech and impaired consciousness and can lead to injury. Long-term effects of use may not only partially mimic schizophrenia as is the case with PCP, but may also lead to a more subtle permanent cognitive disorder with deficits of memory and mood. A nasal form of the drug recently has been approved in some countries for the treatment of refractory depression; whether this will lead to increased abuse as the drug becomes more readily available remains to be seen.

DEXTROMETHORPHAN

Dextromethorphan has been used for decades as a cough suppressant but has emerged more recently as a recreational drug of abuse, especially among teenagers due to its stimulant and dissociative properties.[12] At high doses, dextromethorphan can present with PCP-like effects on NMDA receptors. Patients

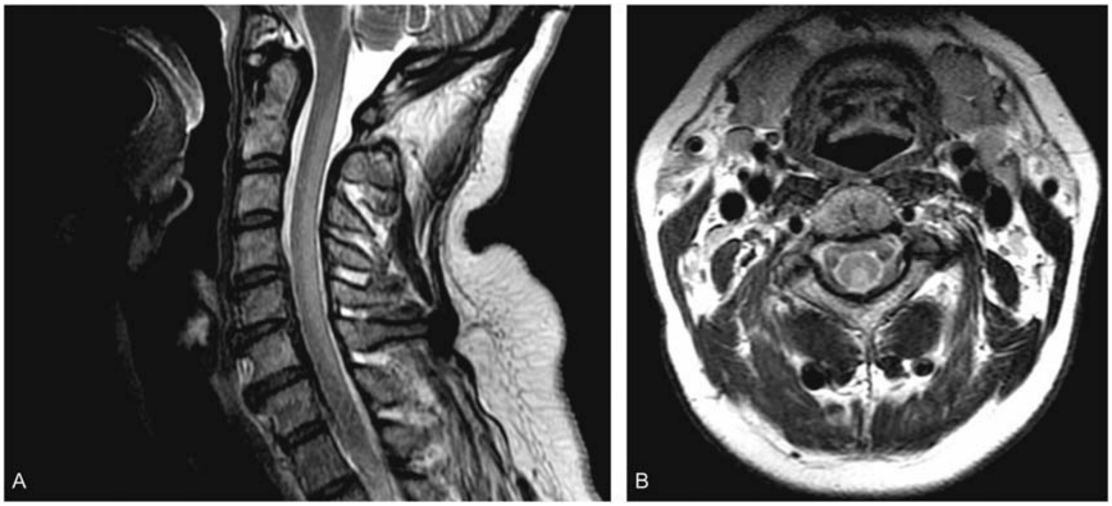

FIGURE 34-3 ■ Sagittal (*A*) and axial (*B*) T2-weighted MR images of the cervical spine in a 51-year-old woman presenting with gait difficulties and ataxia following a 6-month history of recreational nitrous oxide abuse. Hyperintensity is demonstrated in the posterior portion of the cord, corresponding to the location of the dorsal column pathways.

may present with hallucinations, agitation, and ataxia; although in its extreme form coma can result. Elevated blood pressure and heart rate are common along with stimulant and perceptual effects similar to psilocybin. Serotonin syndrome can result from overdose, especially when combined with other serotonergic agents. Widespread abuse of the drug has led to regulatory controls in many states of over-the-counter sale of dextromethorphan-containing compounds.

NITROUS OXIDE

Nitrous oxide is often used recreationally by inhaling the gas from a balloon ("whippet") or other canisters such as those that deliver whipped cream, where the gas is used as a propellant. Although commonly used by young people recreationally, abuse among health-care providers with access to nitrous oxide, such as among those in the dental field, is also well documented.[13] The neurologic manifestations result from effects on vitamin B_{12} pathways. Under normal conditions, nitrous oxide converts vitamin B_{12} to an inactive form that inhibits a key enzyme used in DNA and RNA synthesis, methionine synthase. Patients present with similar symptoms and signs to those occurring with vitamin B_{12} deficiency, although the serum B_{12} level may be normal. Some patients who are exposed to nitrous oxide anesthesia may develop a similar syndrome if they have pre-existing vitamin B_{12} deficiency from, for example, pernicious anemia.

Central nervous system manifestations include psychosis and cognitive decline, but far more common is a myeloneuropathy with prominent posterior column signs. MR imaging may demonstrate increased T2 signal in the posterior columns, often with a predilection for the cervical spinal cord (Fig. 34-3). Patients present with a sensory ataxia, decreased vibratory and proprioceptive thresholds, and a spastic gait with or without weakness of the limbs. Some of these abnormalities can be reversed with vitamin B_{12} supplementation and abstinence from nitrous oxide use, but chronic users may not seek medical attention until the condition is irreversible.

MARIJUANA AND RELATED COMPOUNDS

Tetrahydrocannabinol (THC) is the principal active component of marijuana, which is typically smoked recreationally but can also be consumed orally, where its effects are more delayed. Marijuana use typically leads to euphoria as well as a decrease in anxiety and perceptual changes that can involve slowing of time and vivid colors. There may be relatively mild psychedelic effects in comparison with the hallucinogen class of drugs. Intoxicated patients demonstrate decreased coordination and gait along with psychomotor slowing that can impair safe driving. Some reports have rarely associated marijuana use with stroke, presumably on the basis of vasoconstriction as the likely mechanism. Some chronic heavy users may develop a withdrawal syndrome of irritability, fatigue, anxiety, and difficulty sleeping.

Chronic users of the drug may exhibit an amotivational syndrome characterized by apathy and lack of ambition and drive. It is unclear from the literature whether heavy users of marijuana can develop more permanent cognitive sequelae including deficits of executive function, memory, and attention.[14] Marijuana users appear to be at increased risk of developing psychotic disorders or affective symptoms, but these studies may be confounded by any underlying psychiatric disorder (or tendency) leading to marijuana or other drug use. The increased availability of this substance due to changes in state and federal laws in some jurisdictions will lead to increased focus on both beneficial and adverse events in the coming decade.

The terms “Spice” or “K2” are brand names used to describe a variety of herbal medicines that are widely available and mimic the effects of marijuana.[15] These synthetic compounds may be labeled as “incense” or “herbal smoking products” and have only recently been banned from over-the-counter sale in the United States. Although these drugs resemble cannabinoids, they are often not detectable in the usual screens for THC in the urine; emergency medical personal should be aware of these drugs in patients presenting with symptoms and signs of marijuana intoxication with negative drug screens.

INFECTIOUS COMPLICATIONS OF INJECTION DRUG USE

Many of the recreational drugs discussed here are administered intravenously, and the risk of infectious complications is substantial. This risk is due not only to sharing of needles with associated bacterial and viral contaminants, but also to a lack of sterile technique that can introduce skin flora and other nearby bacteria into the blood stream.

Endocarditis remains an important cause of stroke and cerebral abscess among those with intravenous drug abuse. *Staphylococcus* and *Streptococcus* species are particularly common culprits. Embolic ischemic strokes from endocarditis have a propensity for hemorrhagic transformation, and septic emboli should be considered in patients presenting with multiple hemorrhagic strokes. Subarachnoid hemorrhage may result from ruptured mycotic aneurysms. Those that are ruptured should be secured, usually via surgical clipping; unruptured mycotic aneurysms that are stable are usually treated with antibiotics alone, despite the lack of good data supporting this practice. Intracerebral abscess is a dreaded complication that usually begins as a less walled-off cerebritis, occasionally in the setting of endocarditis; early surgical management is typically recommended along with administration of broad-spectrum intravenously administered antibiotics with good penetration across the blood−brain barrier.

Bacteremia can also lead to seeding of the spinal column and thus to discitis, osteomyelitis, and epidural abscess, important considerations when patients with a history of intravenous drug use present with new back pain, with or without fever. MR imaging is the modality of choice for the spinal cord, and surgery with intravenous administration of antibiotics is the preferred treatment when clinical signs of spinal cord compression are present.

Sharing of needles can also lead to infections such as with human immunodeficiency virus, human T-lymphotropic virus types 1 and 2, and hepatitis virus. Their neurologic presentations are discussed in Chapters 42 and 43. Clinicians need to be aware of these infections and their neurologic complications in patients with a history of intravenous drug use.

CONCLUDING COMMENTS

Neurologic complications of drug abuse continue to be common, and knowledge of these substances and their effects, both during intoxication and with chronic use, is essential for evaluation of patients presenting with neurologic disorders. Because new substances and methods of ingestion are continually emerging, physicians should remain familiar with current recognition and management decisions in this rapidly changing field.

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CHAPTER

35

Neurotoxin Exposure in the Workplace

MICHAEL J. AMINOFF

MANIFESTATIONS OF OCCUPATIONAL NEUROTOXIC DISORDERS
- Acute Encephalopathy
- Chronic Encephalopathy
- Peripheral Neuropathy

SCREENING AT-RISK WORKERS
- Clinical Evaluation
- Electrodiagnostic Testing and Neuroimaging
- Neuropsychologic Evaluation
- Other Laboratory Testing

SELECTED NEUROTOXIC DISORDERS
- Organic Solvents
  - *Central Effects*
  - *Peripheral Neuropathy*
- Heavy Metals
  - *Lead*
  - *Arsenic*
  - *Mercury*
  - *Manganese*
- Organophosphate and Carbamate Pesticides
  - *Early (Type I) Syndrome*
  - *Intermediate (Type II) Syndrome*
  - *Delayed Syndrome: Polyneuropathy*
  - *Prolonged Low-Level Exposure*
- Organochlorine and Pyrethroid Insecticides
- Pesticides, Herbicides, and Parkinsonism

CONCLUDING COMMENTS

Occupationally related disorders are commonly due to injury or to working conditions that involve physical strain, such as hand-arm vibration or performing the same movement repetitively. These disorders are not the focus of the present chapter, which is concerned instead with the consequences of exposure to neurotoxins in the workplace. Many of the chemical agents present in the workplace environment may produce behavioral, cognitive, motor, sensory, or autonomic disturbances resulting from disorders of the central or peripheral nervous system (CNS or PNS). Exposure to such neurotoxic substances may affect workers using them or involved in their manufacture as well as those exposed in industrial, agricultural, horticultural, or military settings. The occurrence of such occupationally related neurotoxic disorders has been known for centuries, but their prevalence is unknown.

In order to demonstrate that a particular chemical is neurotoxic or that a certain syndrome is due to neurotoxin exposure, it must be shown that the suspected neurotoxin causes neurologic dysfunction of a consistent nature in exposed humans. The disorder occurring in one subject must be consistent in character with that occurring in others exposed to the same chemical agent. The neurologic manifestations must be related temporally to exposure to the presumed toxin, and their subsequent course should accord with the biologic properties of that toxin. In other words, the clinical disorder must be biologically plausible. The nature of the toxin and the intensity of exposure will determine how soon after exposure any symptoms develop. The neurologic dysfunction may vary in severity between individuals but—depending on their level of exposure—all exposed workers should have some signs of neurotoxicity. Involvement of a single worker suggests that the disorder is not due to a toxin, that toxin exposure did not occur at work, or that exposure resulted from some individual work habit, such as failure to use a protective mask. Diagnosis of an occupationally related neurotoxic disorder may be difficult when symptoms are common and nonspecific and may occur for a variety of reasons. Moreover, once a neurotoxic disorder is suspected, identical symptoms may develop in suggestible subjects with little or no exposure to the presumed toxin.

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Ideally, to establish the toxic basis of a neurologic disorder, it should be possible to identify reproducible pathologic or pathophysiologic changes in the nervous system in humans or experimentally in animals, and these should account for the clinical features of the disorder. In practice, it is often not feasible to reproduce a suspected neurotoxic syndrome in animals. Variation in species susceptibility may be responsible, and certain impairments (e.g., cognitive or affective disturbances) are anyway difficult to reproduce in animals. Furthermore, human exposure is often to combinations of several chemicals, which individually may be harmless but in combination lead to neurologic dysfunction. This is because the effects of the different chemicals may be additive or one may potentiate the neurotoxic effects of another, as is illustrated by the effect of adding the nontoxic methyl ethyl ketone to a lowered concentration of the known neurotoxin *n*-hexane, a practice that led in the past to an outbreak of toxic neuropathy.

The temporal profile of the clinical disorder may be informative. Depending on the toxic agent, there is often little or no latent period between the time of exposure and onset of symptoms, but certain toxic neuropathies (arsenic, thallium, organophosphates) occur after a delay on the order of 2 to 3 weeks. Although cessation of exposure may lead to clinical stabilization or improvement, deterioration may continue for some days to weeks after termination of exposure to certain neurotoxins, a phenomenon termed “coasting.”

Improvement of symptoms during periods away from work, such as at weekends or during vacations, may raise the possibility of a work-related exposure to a neurotoxin, but other factors may be responsible, such as anxiety or disputes with co-workers. These various points are summarized in Table 35-1.

TABLE 35-1 ■ Features Suggestive of an Occupational Neurotoxic Disorder

History of exposure to a potential neurotoxin

Pattern of neurologic dysfunction accords with previously reported cases

Exposed co-workers also affected

A temporal relation exists between toxin exposure and onset of symptoms, and between cessation of exposure and arrest of progression (sometimes after coasting)

If the pathologic and pathophysiologic bases of the disorder have been identified, they should be reproducible and account for the clinical disturbance; an animal model of the disorder may exist

Other causes of the disorder have been excluded

Attention must be directed at distinguishing between a neurotoxic and pseudoneurotoxic disorder. The latter may relate to a psychogenic illness or to the coincidental onset or worsening of an unrelated or preexisting disorder. Pseudoneurotoxic disorders may be accompanied or followed by the multiple chemical sensitivity syndrome, and by affective symptoms, lassitude, malaise, and social withdrawal. The underlying pathophysiology is unclear and there is no specific treatment, but any mood disturbance requires treatment.

MANIFESTATIONS OF OCCUPATIONAL NEUROTOXIC DISORDERS

There are usually no specific clinical manifestations of a neurotoxic disorder. The symptoms and signs are frequently indistinguishable from those of other neurologic disorders. General examination may, however, reveal additional features suggestive of a toxic cause, such as the presence of hyperkeratosis and desquamation of the skin of the palms and soles and of Mees lines in the nails of patients with arsenic exposure.

Acute Encephalopathy

An acute encephalopathy is a common but nonspecific manifestation that may consist solely of headache and malaise that settle shortly after exposure is discontinued. With more severe involvement, symptoms may come to include confusion, irritability, poor concentration, impaired judgment, drowsiness, vertigo, tinnitus, sensory complaints, ataxia, weakness or fatigue, and nausea and vomiting. Neurologic examination is usually normal. Neuropsychologic examination may be abnormal but, because recovery is rapid and complete (usually within 24 hours), is rarely performed. With continued exposure, level of consciousness becomes depressed, sometimes leading to coma; seizures may also occur. Recovery is then likely to be more protracted and may be incomplete. The cause of this acute syndrome usually is easy to determine because of the history of exposure, because many workers are affected, and because a variety of other manifestations are common, such as conjunctival, mucosal, and cutaneous irritation, and respiratory difficulties.

Chronic Encephalopathy

The occurrence of a chronic encephalopathy relating to long-term low-level neurotoxin exposure is widely reported but of uncertain validity. Its symptoms include headache, "dizziness," poor concentration, memory impairment, irritability, affective disorders, various sleep disturbances, loss of libido, numbness and paresthesias, and "weakness." Such symptoms are nonspecific in nature, usually mild in degree, but may lead to surprising disability. Examination is typically normal, but ataxia and nystagmus are sometimes found; the results of laboratory and electrophysiologic studies are generally unhelpful or of questionable significance or relevance. Neurobehavioral studies may be abnormal, but often the findings are inconsistent, difficult to interpret in the absence of premorbid baseline studies, and of uncertain relevance. At present, then, whether such an entity truly exists—and its pathophysiologic basis—remains unclear.

Peripheral Neuropathy

Peripheral neuropathy is a better understood consequence of toxin exposure in the workplace. It may occur as a delayed effect of single high-dose exposure or after short-term repeated exposure to certain organophosphates, arsenic, or thallium. Chronic exposure to these and other neurotoxins, such as acrylamide and many organic solvents, also leads to neuropathy, causing that portion of the axon farthest from the cell body to degenerate, a phenomenon described as a *distal axonal neuropathy* or *axonopathy*, or a *dying-back neuropathy*. Its clinical features are similar to those of neuropathies of other etiologies. Symptoms and signs begin distally in the legs and then progress proximally depending on the severity of exposure. Sensory axons pass both peripherally to the limbs and centrally into the spinal cord; both degenerate toward the cell body. Some of the central sensory fibers ascend in the posterior columns to the cuneate and gracile nuclei in the medulla and, because of their length, are often among the first to degenerate. As regeneration does not occur in the CNS, recovery after axonal degeneration will be incomplete despite effective regeneration of the peripheral nerves.

The presence of abnormalities on general examination may help to suggest a toxic cause of the neuropathy. For example, sweating and bullous dermatitis of the hands is found in acrylamide toxicity, and scalp alopecia occurs with thallium poisoning.

In subjects who are chronically exposed to other neurotoxins in the workplace but who have no clinical deficit, minor electrodiagnostic abnormalities are sometimes found. Although these will not necessarily progress to clinical neuropathy, such subjects need careful monitoring to limit exposure and minimize any risk of progression.

SCREENING AT-RISK WORKERS

Screening workers for signs of toxicity may help to identify individuals with incipient or subclinical neurologic dysfunction or exposure to low levels of a neurotoxin, and thereby limit further exposure. Screening of fellow workers may also be diagnostically helpful when a subject with a suspected, occupationally related, neurotoxic disorder is encountered, because similarly exposed workers are likely to have at least some symptoms and signs of intoxication, although to a varying degree that probably relates to differences in age, gender, ethnicity, genetic background, health status, and other factors. In general, however, screening techniques are insensitive and poorly tolerated by patients. They are also expensive and time-consuming.

Clinical Evaluation

An occupational history is an important part of the medical record, especially when patients with obscure neurologic disorders are encountered. Job titles may need clarification for the nature of an occupation to be appreciated. If exposure to toxins is suspected, a detailed list of chemicals used in the workplace—and at previous places of employment, if symptoms are longstanding—should be obtained. Details of the work environment are also important, such as whether it is well ventilated, the nature of any protective measures (such as a requirement to wear special clothing and gloves, and the use of other devices including masks and goggles), and the provisions made for washing after exposure and for storage of food. The most common routes of occupational exposure are inhalation and through the skin.

It may be necessary to question co-workers to determine whether they have similar symptoms to those of a subject with a suspected neurotoxic disorder, and even to examine those working in a similar environment. When asymptomatic but exposed co-workers are screened, questioning may be focused, based on the clinical features in recognized cases; self-administered, standardized symptom questionnaires may be especially helpful.

Neurotoxin exposure may also relate to environmental factors (such as a subject's residence or its location close to, for example, an industrial plant) and to social and personal factors (such as hobbies, other recreational activities, or dietary peculiarities) rather than to the workplace. The history must therefore exclude these possibilities.

Routine neurologic examination is of limited utility for screening purposes, its principal role being to exclude other conditions that might underlie the patient's symptoms. Generalized rather than focal neurologic abnormalities are the expected finding in many neurotoxic disorders. In some instances, however, focal findings—such as parkinsonism from manganese exposure—may be conspicuous. Techniques have been developed for quantifying aspects of the neurologic—especially the sensory—examination for screening purposes and for following changes over time. These include quantitative tests of muscle strength, coordination, body sway, balance, vibration and discriminative tactile sensibility, cold and warm thermal thresholds, and heat pain thresholds.

Electrodiagnostic Testing and Neuroimaging

Electroencephalography (EEG) and evoked potential studies can be used to assess CNS function. The EEG is commonly slowed diffusely—but occasionally more focally—in patients with acute toxic or metabolic encephalopathies, but may be normal in chronic encephalopathies. It is therefore of little use in screening patients for neurotoxic injury. Changes are nonspecific and do not distinguish between toxic and other encephalopathies or between different toxic disorders. Evoked potentials provide some measure of the functional integrity of certain afferent CNS pathways, but normal responses may show marked amplitude variation between subjects and on the two sides of the same subject. Because most neurotoxins produce axonal degeneration, which causes changes in amplitude rather than latency of responses, evoked potentials are of limited utility in evaluating patients with suspected neurotoxicity.

Electromyography (EMG) and nerve conduction studies evaluate the function of the PNS, neuromuscular junctions, and muscle. The findings help to identify subclinical disease, follow disease progression, and characterize the pathophysiologic basis of symptoms. Nerve conduction studies are useful in studying both axonal and demyelinating neuropathies. Needle EMG can indicate the cause of weakness and localize pathologic processes to different regions of the motor units (spinal cord, nerve root, plexus, peripheral nerve, neuromuscular junction, or muscle). When evaluating exposed workers, comparison with appropriate control subjects is important. For example, sedentary office workers should not be used as controls for manual workers, who frequently develop minor abnormalities of nerve conduction as a result of occupationally related, repeated minor trauma or subclinical entrapment neuropathies.

Neuroimaging of the CNS, when normal, does not exclude a neurotoxic disorder. In some instances, however, the findings may show characteristic abnormalities, such as in manganese poisoning, discussed later.

Neuropsychologic Evaluation

Advances in neuropsychologic test procedures have improved their utility as a screening device. Such test procedures may reveal subtle cognitive dysfunction but the findings are not diagnostic of toxic encephalopathy. Moreover, testing is time-consuming even when self-administered questionnaires and computerized test procedures are used, and thus costly and impractical for screening large numbers of subjects. Careful matching for age, gender, ethnicity, and social, cultural, and educational background is necessary when making comparisons between groups.

Other Laboratory Testing

Workers with possible occupationally related neurotoxic disorders commonly come to medical attention when exposure has already ceased and laboratory testing is of limited utility. With the exception of screening for heavy metal excretion in the urine or their presence in other tissues, laboratory studies are generally unhelpful in screening for neurotoxic disorders.

SELECTED NEUROTOXIC DISORDERS

Only a limited number of neurotoxins and the disorders that they produce can be discussed in the space available here, and readers seeking more specialized information should consult standard textbooks or compendia on neurotoxicology.

Organic Solvents

Organic solvents, either individually or in combinations, are widely used in the workplace, for example, as cleaners, degreasers, and thinners, and in manufacturing other chemicals. Most are highly volatile liquids. Accordingly, exposure occurs primarily by inhalation, so the risk of toxicity is greatest in poorly ventilated areas. Some absorption also takes place through the skin, especially of those solvents that are both lipid and water soluble and are somewhat less volatile.

Ridgway and co-workers assessed the published evidence that industrial organic solvents as a generic group can induce long-term neurologic damage detectable by brain imaging, neurophysiologic testing, or postmortem studies of exposed workers.[1] Some of the studies provided evidence for marginal atrophic abnormalities in the brain or deficits in nerve conduction velocity in solvent-exposed workers. However, methodologic limitations, absence of a consistently strong association between exposure and effect, lack of a dose–response relationship, the nonspecific nature of the reported changes, and the lack of coherence between the human and experimental animal data were problematic. Overall they were unable to draw reliable conclusions with respect to the presence or absence of nervous system damage related to the common properties of organic solvents.

CENTRAL EFFECTS

Most organic solvents have high lipid solubility, so that they rapidly enter the brain and act as nonspecific depressants of the CNS. Acute exposure can cause the syndrome of acute encephalopathy described earlier. The exposed individual must be removed from exposure; recovery after mild exposure occurs rapidly (minutes to hours), usually without sequelae, although headache may continue for longer. When exposure has led to coma, however, recovery may be incomplete, perhaps because of hypoxic brain damage.

Several epidemiologic studies have suggested that neuropsychologic dysfunction has an increased prevalence in spray painters, who are chronically exposed to solvents used as thinners. Both level and duration of exposure may be important in its development. However, it is unclear whether the entity of painters' encephalopathy truly exists, because it is based on studies, mainly from the 1970s, which are so methodologically flawed that they are invalid. These studies were primarily epidemiologic in nature. Objections to them include concerns about the manner in which neuropsychologic tests were conducted and that other factors (such as alcohol, medications, or the residual effect of acute solvent exposure) may have caused the encephalopathic features ascribed to chronic exposure. Details concerning work conditions and extent of solvent exposure were often not provided or based on subjective recall. Some studies failed to allow for the influence of various confounding factors on neuropsychologic test results. In others, inappropriate controls may have confounded any comparisons that were made. This is well exemplified by the study of Gade and co-workers, in which 20 solvent-exposed workers, mostly painters, were re-examined 2 years after the diagnosis of chronic toxic encephalopathy was made.[2] Neuropsychologic test results were unchanged, but the earlier impression of significant cognitive decline was not confirmed when comparison was now made to a nonexposed control group and allowance was made for age, educational background, and level of intelligence.

Nevertheless, the concept of painters' encephalopathy has come to be accepted by many authorities and diagnostic criteria have been proposed by several working groups and organizations despite the doubts that exist concerning its existence as a specific entity. It appears to be nonprogressive, with no deterioration of functioning—or, in some cases, improvement—occurring after diagnosis, presumably because of cessation of exposure. It is characterized by fatigue, irritability, mood changes, difficulty in concentration, forgetfulness, and impairment in various modalities on neuropsychologic testing. If such a syndrome of chronic painters' encephalopathy exists, it may have been caused by toluene, as most subjects were exposed to solvent mixtures, often of unknown composition, and toluene is a common constituent of such mixtures.

Chronic abuse of toluene in large doses taken for recreational purposes may cause dementia, ataxia, dysarthria, nystagmus, tremor, and spasticity. Magnetic resonance imaging (MRI) shows diffuse cerebral and cerebellar atrophy and widespread periventricular white matter lesions. Brainstem auditory evoked potentials (BAEPs) may be abnormal, even in the absence of clinical or neuroimaging abnormalities, suggesting that the BAEP may be useful for screening at-risk workers. A similar syndrome has not been seen with occupational exposure, perhaps because of the prolonged exposure to very large doses during abuse, but contamination of the solvents with other toxins or the concomitant use of other chemicals and drugs may also be relevant. In any event, the diagnosis of chronic solvent exposure is being made less often, perhaps because exposure to solvent mixtures has declined in developed countries, although many workers remain chronically exposed to such mixtures.[3]

A more persuasive example of toxic encephalopathy with chronic exposure to organic solvents is the chronic encephalopathy that follows long-term exposure to carbon disulfide, used to manufacture cellophane and rayon.

PERIPHERAL NEUROPATHY

Discussion here focuses on *n*-hexane and methyl *n*-butyl ketone (MnBK) because the use of these hexacarbons has led to several outbreaks of neuropathy. Their metabolite, 2,5-hexanedione, is primarily responsible for the distal axonopathy that occurs with repeated and prolonged exposure to *n*-hexane. Methyl ethyl ketone, a common constituent of organic solvent mixtures, potentiates the neurotoxic properties of *n*-hexane and MnBK.

Onset is typically insidious and progression occurs slowly. Numbness begins distally in the feet, spreading proximally with continuing exposure, and then comes to involve the hands. Motor disturbances are less conspicuous but, in severe cases, mild footdrop and weakness of the intrinsic hand muscles develop. With recreational exposure, which is typically heavier than occupational exposure, more rapid progression occurs and symptoms may be more extensive and severe. Examination shows significant cutaneous sensory deficits, and loss or attenuation of muscle stretch reflexes, especially distally. Gradual improvement (by axonal regeneration) eventually follows cessation of exposure, but coasting may occur for a period of several weeks.

Electrodiagnostic screening is useful in the detection of subclinical hexacarbon neuropathy. In a major outbreak of MnBK neuropathy in Ohio, 43 percent of cases had characteristic electrophysiologic abnormalities in the absence of symptoms and signs of neuropathy.[4] Needle electromyography usually showed signs of active denervation in distal leg muscles, and motor conduction velocity was slowed. Pathologically, the neuropathy is characterized by defective axonal transport, axonal degeneration, and secondary demyelination. Such changes may be seen on sural nerve biopsy and are also present at autopsy in the distal (i.e., most rostral) portion of the sensory axons in the posterior columns of the spinal cord.

A distal axonopathy can also result from exposure to trichloroethylene, which has been used as a degreaser. It is confined to the cranial nerves, initially the trigeminal nerve, with early onset of facial numbness, analgesia, or dysesthesias and later weakness of the masticatory muscles. The lower cranial nerves are involved in some patients; optic neuropathy (with an enlarged blind spot, paracentral scotoma, or constricted fields) has also been described. Recovery occurs with time after discontinuation of exposure, but patchy facial sensory loss may persist indefinitely.

Heavy Metals

Heavy metals accumulate, especially in bone, during lengthy periods of low-level exposure, as in the workplace, and it may take years to eliminate them from the body. Heavy metals are neurotoxic but also have other effects, particularly on the hematopoietic and gastrointestinal systems. The present discussion focuses on lead and arsenic, as exposure to these is most likely to occur, on mercury because of the large outbreaks that have occurred in the past (to environmental rather than occupational exposure), and on manganese because of suggestions that it may be a cause of classic Parkinson disease.

LEAD

Industrial exposure is mainly to inorganic lead and occurs by inhalation of fine particulate matter; lead may also be absorbed after ingestion, as occurs in children. Occupational exposure occurs in the construction industry as well as in various other industrial settings (such as lead production or smelting; scrap metal handling; battery manufacturing; lead and other metal foundries; lead soldering; metal radiator repair; firing ranges; and ceramics or plastics manufacturing). Lead is taken up into bone and then slowly released into the blood over many years and excreted primarily through the urine, with smaller amounts in feces, hair, nails, and sweat.

There is increasing concern about the health effects of lead at blood levels once thought to be harmless. For example, a causal relationship of low-level lead exposure to hypertension has been found, with implications for stroke prevention, as has an association with declining cognitive function and with the development of amyotrophic lateral sclerosis. Preliminary studies suggest also that cumulative exposure to lead increases the risk of Parkinson disease. Recent studies have led to a reappraisal of the levels of lead exposure that may be safely tolerated in the workplace.[5] It is important that workers are in well-ventilated premises; wear appropriate personal protective equipment such as goggles, boots, special clothing, and proper respiratory protection; shower after work; and undergo routine determination of blood lead level.

Lead Encephalopathy

Acute occupational exposure to lead results mainly in systemic effects involving the hematopoietic, gastrointestinal, and renal systems, rather than the nervous system. An acute lead encephalopathy, resulting from increasing cerebral edema, tends to occur in children rather than exposed workers and is therefore not considered further here. A chronic encephalopathy may follow long-term exposure to low levels of lead, and progressive cerebral atrophy can occur long after further exposure is prevented.[6] Symptoms may include apathy, fatigue, insomnia, reduced libido, headache, irritability, memory loss, and difficulty in concentration; testing reveals neuropsychologic and neurophysiologic abnormalities.

Lead Neuropathy

Chronic exposure (i.e., for several years) to lead causes neuropathy. In one study, the average duration of exposure in subjects with lead neuropathy was almost 22 years. Nerve conduction slowing may occur earlier, increasing with duration of exposure and blood lead levels, but whether these neurophysiologic changes progress to overt neuropathy is unclear.

Lead neuropathy, when it develops subacutely, is unusual in that it is predominantly motor, often asymmetric, and affects the arms more than the legs, and the wrist and finger extensors more than other muscles. Wrist drop is characteristic. This form of neuropathy typically develops after a relatively short period of intense exposure.[7] A more typical toxic neuropathy, with distal sensory impairment and weakness, may also occur, however, especially after prolonged exposure.[7] Individuals with lead neuropathy generally have a microcytic, hypochromic anemia; basophilic stippling of red blood cells is not always present and is not specific for lead poisoning. In patients with continuing exposure to lead, neuropathy is unlikely if the urinary δ-aminolevulinic acid (δALA) is normal. Lead interferes with hemoglobin synthesis by inhibiting the enzyme δALA dehydrase, and the enzyme substrate begins to appear in the urine when the blood lead level reaches 40 to 50 μg/dL, which is less than the level at which neuropathy usually results. An increased blood lead level or increased 24-hour urinary excretion should also be present in patients with suspected lead neuropathy, provided that exposure to lead is ongoing. When the blood lead level is mildly elevated ($>$ 25 μg/dL), it may be helpful to measure free erythrocyte protoporphyrin or zinc protoporphyrin, which reflect the inhibitory effect of lead on enzymes involved in hemoglobin synthesis and thus the lead exposure over the preceding 3 months. Past excessive exposure to lead can be measured through its accumulation in teeth or bones, but this is seldom practical.

The pathophysiologic basis of lead neuropathy in humans is unknown. There are species differences in the effects of lead on the nervous system. The early development of slowed conduction velocity suggests that the primary pathologic process is demyelination, but in established neuropathy the predominant abnormality is axonal degeneration.[7]

Management involves removal of the individual from the toxic environment to prevent further exposure. Workers exposed to lead occupationally should undergo regular determination of the blood lead level, and exposure terminated in those with an increased level before neuropathy develops. The blood lead level reflects the amount of lead in the blood and soft tissues but does not indicate either previous or current exposure, or total body burden. National and state guidelines indicate surveillance requirements (including blood level monitoring requirements) for at-risk workers, such as those of the California Department of Public Health Occupational Lead Poisoning Prevention Program. Based on a literature review and their own experience in evaluating lead-exposed adults, Kosnett and colleagues recommended in 2007 that subjects should be removed from occupational lead exposure if a single blood lead level exceeds 30 μg/dL or two successive blood lead levels measured over a 4-week interval exceed 19 μg/dL.[5] Removal of individuals from lead exposure should be considered to avoid long-term risk to health if exposure control measures over an extended period do not decrease blood lead concentrations to less than 10 μg/dL or if selected medical conditions exist that would increase the risk of continued exposure. They recommended that medical surveillance for all lead-exposed workers should include quarterly blood lead measurements for individuals with blood lead concentrations between 10 and 19 μg/dL and semiannual blood lead measurements when sustained blood lead concentrations are less than 10 μg/dL. The aim should be to maintain the blood lead levels of exposed workers below 20 μg/dL, and preferably below 10 μg/dL.

It is unclear whether chelation therapy, which accelerates removal of lead from the blood and soft tissues (but less so from bone), benefits the clinical neuropathy. Clinical trials are lacking. Guidelines are controversial and liable to change. One therapeutic approach has been with EDTA; another oral agent, 2,3-dimercaptosuccinic acid (DMSA; succimer), seems equally effective and can be used alone or after EDTA. Regardless of the treatment chosen, it should be continued until a steady-state level of lead excretion has been achieved. In patients with large lead stores in bone, chelation may be followed by movement of lead from bone back into the blood and soft tissues, leading to a rebound increase in blood lead level after an initial drop. Chelation therapy is not appropriate for workers with continuing lead exposure as prophylaxis against rising blood lead levels.

ARSENIC

Arsenic intoxication may occur occupationally but more commonly by ingestion of contaminated food or water. It may relate to attempted homicide. Occupational exposures may occur in the manufacture of paints, fungicides, wood preservatives, and semiconductors; in certain mining and smelting operations; from combustion of arsenic-containing coal or incineration of certain preserved wood products; and in pesticide spraying. A hemorrhagic encephalopathy and various systemic effects (including QTc prolongation on the electrocardiogram and subsequent ventricular tachycardias) occur with acute intoxication; the role of arsenic in the development of a chronic encephalopathy is controversial. Arsenic leads to a peripheral neuropathy that is a predominantly sensory, distal axonopathy and occurs after exposure to high levels of arsenic, usually by ingestion with suicidal or homicidal intent, or after long-duration low-level exposure. Chronic exposure is associated also with an increased risk of skin and various other cancers. Acute intoxication leads to prominent gastrointestinal symptoms followed, after 1 to 3 weeks, by the onset of neuropathy. Numbness, burning, and paresthesias begin in the feet and spread to the legs, hands, and arms. Pain is sometimes prominent. Sensory ataxia occurs in severe cases. Weakness is usually mild and overshadowed by the sensory disturbances, but marked weakness and respiratory insufficiency may occur with severe intoxication. Autonomic instability is usually a minor feature. Examination confirms that there is symmetrical, distally conspicuous sensory loss and weakness.

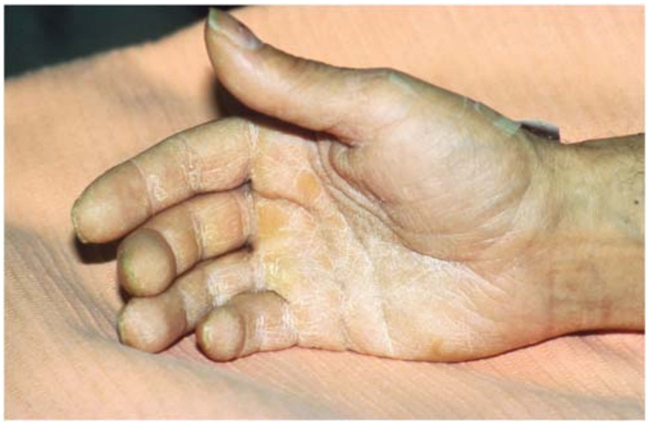

FIGURE 35-1 ▪ Hyperkeratosis and desquamation of the skin of the palms of the hands from arsenic toxicity. (Courtesy of J. Richard Baringer, MD, University of Utah.)

Other toxic effects of arsenic accompany the neuropathy and include hyperkeratosis and desquamation of the skin, particularly in the palms (Fig. 35-1) and soles; redness and swelling of the hands and feet; patchy areas of skin discoloration with chronic intoxication; and, particularly with acute poisoning, transverse gray lines in the nails (Mees lines; Fig. 35-2). Kidney failure may occur. Anemia is common, and red blood cells may show basophilic stippling.

An acutely evolving neuropathy may be misdiagnosed as Guillain–Barré syndrome, especially if the

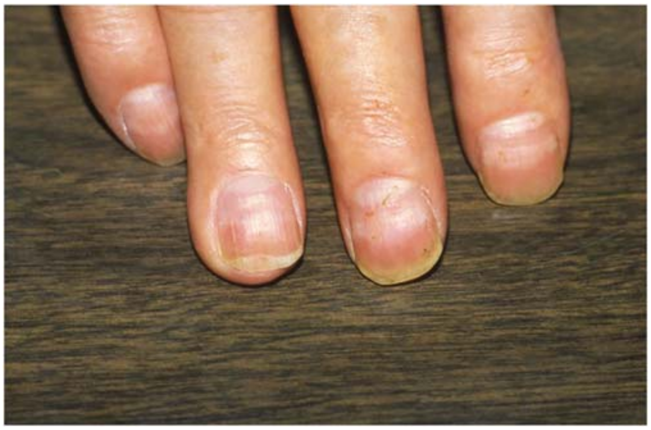

FIGURE 35-2 ▪ Transverse gray lines in the nails (Mees lines) related to arsenic toxicity. (Courtesy of J. Richard Baringer, MD, University of Utah.)

initial gastrointestinal symptoms are mistaken for a prodromal illness and the cerebrospinal fluid shows an albuminocytologic dissociation, as sometimes occurs in early arsenic neuropathy. The electrodiagnostic findings may also resemble those of Guillain–Barré syndrome because the underlying axonal degeneration is accompanied by proximal demyelination. The diagnosis requires the demonstration of arsenic in blood, urine, or tissues. Measurement of blood levels is usually diagnostically unhelpful because arsenic is cleared very rapidly, but urinary excretion is increased for weeks. The most reliable means of monitoring exposure in at-risk occupations is by determining the 24-hour urinary arsenic level, which should be determined after subjects have abstained from eating fish, seaweed, or shellfish for 48 to 72 hours. Arsenic is cleared from blood into tissues; for example, it comes to be bound to keratin of growing hair or nails and may be found in slow-growing hair, such as pubic or axillary hair, for months or even years after exposure. This is important when exposure is not suspected until long after the event. The results of such analyses when performed in commercial laboratories, however, may be inaccurate.

Treatment consists of removing the subject from further exposure. Removal of clothing and cleaning the skin and hair to prevent further contamination are particularly important in those exposed to pesticides. Chelation therapy hastens the excretion of arsenic, but there is no evidence that it increases the rate of recovery from neuropathy, which takes months to years. Patients with mild neuropathy may recover completely, but those with a severe neuropathy are likely to have a residual deficit.

MERCURY

Both organic and inorganic mercury may cause toxicity. Ingestion of methyl mercury in contaminated food such as fish leads to optic neuropathy, hearing loss, cerebellar deficits, and cognitive or behavioral changes. There are also prominent sensory abnormalities that are probably central in origin. Exposure to organic mercury should be stopped and a 24-hour urine sent for measurement of mercury concentration. There is no effective treatment and neurologic damage is likely to be permanent.

Inorganic mercury is mainly absorbed by inhalation during smelting, which is the major means of occupational exposure. Occupational exposure also occurs in chloralkali plants, during mining operations, during the manufacture of medical appliances, glassware, and jewelry, and in dental offices during the preparation of fillings. Ingestion of mercury-containing medications is also sometimes responsible for toxicity. Inorganic mercury may produce a variety of general medical disorders including gastrointestinal symptoms and nephrotic syndrome.

Neurotoxicity is common in the workplace with exposure to mercury vapor levels exceeding 50 μg Hg/m^3. It can manifest as a toxic encephalopathy. The past use of mercury in felt hat production led to many symptoms of high-level mercury neurotoxicity, and thus to the popular phrase “mad as a hatter.” Signs include irritability, anxiety, agitation, social withdrawal, and insomnia; continuing exposure leads to development of a fine tremor of the hands (“hatter’s shakes”) and then of the facial muscles and tongue. In mild cases, encephalopathy and tremor improve gradually over several years once exposure is discontinued. Peripheral neuropathy resembling an inflammatory polyneuropathy has also been attributed to exposure to both forms of mercury, but with only limited supportive evidence. The neuropathy may still be detected many years after the end of exposure, depending on its severity. The diagnosis is confirmed by measuring the blood mercury and 24-hour urinary mercury levels. Exposure should be discontinued, supportive care ensured, and for acute poisoning (typically by ingestion) chelation therapy can be considered, depending on severity.

MANGANESE

Inhalation of dust or vapor during the mining or smelting of manganese may lead to intoxication. Occupational exposure also occurs in manganese alloy producers, cell-battery factory workers, and farmers using manganese-containing fungicides. As much of the dietary intake of manganese is cleared by the liver, liver failure or even asymptomatic hepatitis may precipitate manganese neurotoxicity in exposed workers. The earliest manifestation is a toxic psychosis, with behavioral and cognitive abnormalities; headache, dysarthria, tremor, and incoordination may develop later. Extrapyramidal changes, with dystonia (such as involuntary plantar flexion of the feet) or parkinsonism (abnormalities of gait and balance, bradykinesia, rigidity, rest and action tremor, hypomimia) may eventually develop. A characteristic “cock-gait” is described. After exposure is terminated, early behavioral changes may stabilize and reverse, but extrapyramidal deficits may continue to progress for several years before reaching a plateau.[8]

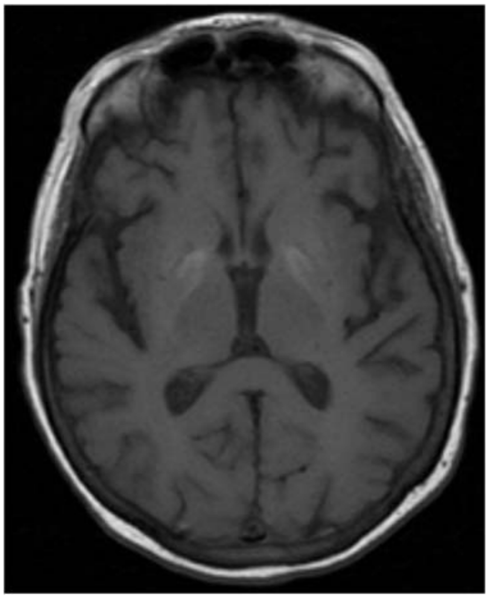

FIGURE 35-3 ■ Bilateral globus pallidus hyperintensity in T1-weighted axial MRI suggestive of manganese accumulation. (Courtesy of William P. Dillon, MD, University of California, San Francisco.)

MRI, positron emission tomography (PET), and single-photon emission computed tomography (SPECT) have been used to study manganese-induced parkinsonism. T1-weighted MRI (Fig. 35-3) shows increased signal intensity in the globus pallidus and midbrain bilaterally in exposed workers who are either asymptomatic or have signs of manganese intoxication. [^{18}F]dopa PET and SPECT are normal, indicating the integrity of the nigrostriatal dopaminergic system. Thus, the damage in manganese toxicity is presumably downstream of the nigrostriatal system, and this would account for the poor response to levodopa in such patients.

Manganese-induced parkinsonism is distinguished from classic Parkinson disease by the history of manganese exposure, usually symmetric clinical features, neuroimaging findings (abnormal T1-weighted MRI and normal fluorodopa PET and SPECT scans), and poor response to levodopa.[9] There are also pathologic differences at autopsy.[9] Exposure to manganese in low dose, as in welders, has been incriminated as a risk factor for the early onset of Parkinson disease, but no relationship between welding and Parkinson disease could be identified in other studies.

Organophosphate and Carbamate Pesticides

Organophosphates and carbamates are used as pesticides or herbicides, and some organophosphates have also been used for terrorism or as warfare agents. Inhibition of acetylcholinesterase (AChE) accounts for their early acute toxicity, and inhibition of neuropathy target esterase (NTE) relates to the delayed neuropathy that occurs after exposure to some of them. Although inhibition of NTE is necessary for the development of peripheral neurotoxicity, not all organophosphates that inhibit NTE cause neuropathy; other factors are also involved. Different organophosphates have differing potencies against these enzymes, although almost all have some anticholinesterase effects. Most organophosphates and carbamates are readily absorbed transdermally during and after spraying, as well as by inhalation and ingestion.

EARLY (TYPE I) SYNDROME

The earliest manifestations represent inhibition of AChE at CNS cholinergic and postganglionic parasympathetic receptors (Table 35-2). The CNS effects are characterized by behavioral changes, mainly agitation, and may progress to convulsions, obtundation, and even coma, which sometimes has a delayed onset. Life-threatening peripheral muscarinic effects include bradycardia and hypotension, or even complete cardiovascular collapse. Bronchospasm, increased secretions, and pulmonary edema can occur. Less threatening peripheral muscarinic effects include meiosis, diarrhea, urinary urgency or incontinence, and increased salivation, lacrimation, and sweating. Muscle fasciculations and weakness reflect nicotinic (neuromuscular junction) effects. In severe intoxication, death occurs from respiratory failure or cardiac arrhythmias.

The speed and extent of inhibition of AChE govern the onset and severity of the clinical disorder. Muscarinic features typically appear first and are most obvious except in severe toxicity, when nicotinic features may be especially conspicuous. The cholinergic effects of organophosphate poisoning usually begin within hours of exposure. AChE inhibition by carbamates is reversible, and symptoms and signs of carbamate toxicity are generally less severe and of shorter duration than with organophosphate poisoning.

Diagnosis is clinical and is suggested by signs of cholinergic overactivity. Electrodiagnostic studies initially reveal repetitive firing of the compound muscle action potential after a single stimulus to the motor nerve, and later a decremental muscle response to repetitive nerve stimulation. Measurement of AChE activity in plasma or red blood cells to confirm suspected intoxication or to monitor exposed subjects is of dubious value.

TABLE 35-2 ■ Effects of Organophosphate Poisoning

Muscarinic Effects

Respiratory
- *Smooth muscle (contraction):* bronchoconstriction; dyspnea
- *Glandular secretions (increased):* rhinorrhea; bronchorrhea; pulmonary edema
- *Multifactorial:* cough; dyspnea

Cardiac
- *Conducting system:* bradycardia; arrhythmias; heart block

Gastrointestinal
- *Smooth muscle (contraction):* nausea; vomiting; abdominal cramps; diarrhea
- *Secretions (increased):* nausea; vomiting; diarrhea
- *Sphincter (relaxation):* fecal incontinence

Urinary bladder
- *Smooth muscle (contraction):* frequency; urgency
- *Sphincter (relaxation):* urgency; incontinence

Eye
- *Contraction of iris and ciliary muscle:* meiosis; blurred vision

Other
- *Secretions (increased):* sweating; salivation; lacrimation

Nicotinic Effects

Skeletal muscle
- *Excitation:* fasciculations; cramps; followed by weakness, paralysis; areflexia

CNS Effects

Excitation: agitation; anxiety; headache; ataxia; confusion; delirium; behavioral abnormalities; convulsions

Depression: obtundation; coma; respiratory depression

Prompt treatment is essential. Continuing exposure should be stopped, for example, by removing contaminated clothing when dermal exposure is likely. Respiratory and circulatory functions must be maintained. Atropine blocks the binding of acetylcholine (ACh) to muscarinic receptors; a test dose of 0.5 mg intravenously causes tachycardia and mydriasis in normal subjects but has little effect in organophosphate-intoxicated subjects. After this, 1 mg is administered intravenously and repeated every 10 to 20 minutes until clinical evidence of atropinization is achieved, and bronchorrhea and rhinorrhea are controlled. It is then maintained for 24 to 48 hours. In severe cases, continuous intravenous infusion of atropine is required. Patients should be managed in the intensive care unit because atropine can precipitate cardiac arrhythmias, especially in the setting of hypoxemia. Atropine has no effect on nicotinic neuromuscular receptors and thus fails to help any weakness or respiratory impairment, and similarly does not influence the CNS effects (agitation and convulsions).

Reactivators of phosphorylated AChE, such as pralidoxime, are also utilized in organophosphate poisoning, but are of uncertain benefit. Effectiveness is independent of receptor type. The complex that forms between the organophosphate and cholinesterase is initially reversible, but subsequently configurational changes occur, and pralidoxime is then ineffective. Treatment is started early with pralidoxime (1 g) intravenously; in the absence of improvement, the dose is repeated after 30 minutes or continuous infusion is commenced at 0.5 g/h. Treatment with oxime is not necessary for carbamate poisoning, because spontaneous reactivation of AChE occurs rapidly. A benzodiazepine is given to allay anxiety and for anticonvulsant effect and supportive therapy with other anticonvulsants may also be needed.

Prognosis depends on the severity of poisoning and on how it is managed. Neurobehavioral sequelae unrelated to structural brain damage have been noted after recovery from acute poisoning. It is unclear whether long-term low-level exposures to anticholinesterases have neurologic or behavioral consequences.

INTERMEDIATE (TYPE II) SYNDROME

This occurs a few days after exposure in up to 50 percent of cases of severe organophosphate poisoning. Its pathogenesis is unknown, but it may relate to a persistent excess of ACh at the neuromuscular junction.[10] It does not respond to atropine or pralidoxime. Presentation is with acute respiratory failure, weakness of neck flexors and proximal limb muscles, and cranial neuropathies. An acute, reversible extrapyramidal disorder has also been attributed to organophosphate poisoning following massive exposure. Treatment is supportive. Recovery may take several weeks.

The intermediate syndrome rarely—if ever—occurs after carbamate insecticide poisoning.

DELAYED SYNDROME: POLYNEUROPATHY

Certain organophosphates cause a distal, predominantly motor, subacute axonal neuropathy that manifests about 1 to 3 weeks after exposure. With those insecticides currently in use, the neuropathy follows an episode of severe cholinergic toxicity.[10] It is unclear whether neuropathy also follows severe carbamate intoxication.[10] The neuropathy relates to inhibition of NTE, followed by "aging" of the phosphoryl−NTE complex, but how this leads to development of the neuropathy is unknown.

The usual initial symptoms are of cramping muscle pain in the calves, followed by distal paresthesias in the feet. Lower-extremity weakness and areflexia then occur, beginning distally and spreading proximally. The upper limbs are involved in severe cases, but the cranial nerves are not affected. Progression occurs over 2 or 3 weeks, followed by gradual improvement. CNS involvement is common after severe exposure but is obscured initially by the peripheral neuropathy; spasticity and ataxia become apparent as the neuropathy improves. Organophosphate toxicity should be considered in any subacute, progressive distal axonopathy even in the absence of a history of exposure. The electrodiagnostic findings are abnormal but nonspecific. There is no specific treatment.

Carbamates are generally held not to be associated with delayed polyneuropathy.[10] A few incompletely reported cases of delayed polyneuropathy in this context have been published, but it is uncertain whether these related to carbamate toxicity.

PROLONGED LOW-LEVEL EXPOSURE

There is no convincing evidence that prolonged low-level exposure to organophosphates causes delayed or any other type of neuropathy.[10] The evidence is also conflicting whether low-level occupational exposure to organophosphates affects neurobehavioral function. A meta-analysis of 14 studies assimilated data from more than 1,600 participants and found a significant association between low-level exposure to organophosphates and impaired cognitive functions such as psychomotor speed, executive function, visuospatial ability, and working and visual memory.[11]

Organochlorine and Pyrethroid Insecticides

Dichlorodiphenyltrichloroethane (DDT) and various organochlorines, such as aldrin, dieldrin, and lindane, were previously used widely as insecticides. Because of their slow degradation, they persist for long periods in animals and the environment. Their use is now banned. Decline in neurobehavioral functioning and increase of neuropsychologic and psychiatric symptoms have been reported in retired DDT workers. Cognitive performance deteriorated with increasing duration of exposure to DDT. Although such data suggest that exposure to DDT may be associated with permanent decline in neurobehavioral functioning, the limited number of studies and uncertainties about exposure levels prevent a firm conclusion from being drawn. Because organochlorine pesticides are potent tremor-producing agents, exposure to DDT, dieldrin, and certain other chlorinated hydrocarbons has been examined as a possible etiologic factor for the development of essential tremor, but no association was found. Similarly, studies in animals have failed to show any effect of DDT or dieldrin on the nigrostriatal system, making unlikely a relationship between exposure to these insecticides and development of Parkinson disease.

Chlordecone, another persistent chlorinated hydrocarbon, was involved in a major industrial exposure and environmental contamination in the 1970s from a manufacturing plant in Hopewell, Virginia. Some workers developed a neurologic illness from dust inhalation, characterized by postural and intention tremor (primarily of the hands but sometimes affecting the head or entire body), opsoclonus, clumsiness, slurred speech, and mild gait ataxia. Mood changes, irritability, and memory loss also occurred. Idiopathic intracranial hypertension occurred in a few cases. Recovery occurred slowly over several years and was sometimes incomplete.[12] Use of chlordecone is now banned.

Pyrethrins are now preferred over organophosphates or organochlorines as pesticides because of their biodegradability. They occur in the seed cases of the perennial plant *Pyrethrum*, and have been synthesized to produce the pyrethroid insecticides. DDT, the pyrethrins, and the synthetic pyrethroids (which account for about 20% of the world insecticide market) act on the voltage-gated sodium channel proteins of insect neuronal membranes. Transmission of nerve impulses is disrupted by binding of the insecticides, leading to paralysis and eventual death.

Occupational exposure to pyrethroids occurs primarily through the skin but sometimes by inhalation in professional sprayers for agricultural purposes or to control vectorborne diseases. Reports of human poisoning are relatively few. Pyrethroid toxicity in humans causes paresthesias affecting the face and hands. This has been attributed to an effect on voltage-dependent sodium channels, resulting in prolonged inward sodium currents leading to repetitive firing and subsequently to membrane depolarization. There is no correlation between the occurrence of paresthesias and urinary excretion of pyrethroids or their metabolites. Paresthesias generally disappear within 24 hours and there is no specific treatment. Other common symptoms are "dizziness," headache, and fatigue; palpitations, chest tightness, and blurred vision are less frequent. Coma and convulsions occur in rare instances and may then be life-threatening.

A slowly progressive motor neuron disease simulating amyotrophic lateral sclerosis has been reported after heavy and prolonged exposure to various pyrethroids and to organochlorines, but further studies of such possible associations are required before any conclusions can be reached about their significance.

Pesticides, Herbicides, and Parkinsonism

The pathogenesis of Parkinson disease probably involves both genetic and environmental factors. Case-control studies in humans have related parkinsonism to farming, rural living, and well-water consumption. Pesticide exposure is one risk factor for developing the disease, but it is difficult to expand on this effect. Exposures typically occur many years before the development of clinical parkinsonism, probably involve several pesticides that may have had additive effects, and often are of unknown duration and severity. Genetic factors may affect the response to environmental factors. Furthermore, toxin-mediated effects may remain clinically silent until normal age-related dopaminergic cell loss reaches a certain critical level, accounting for the delay between exposure and clinical disease.

Parkinsonism has developed in humans who took methylphenyl tetrahydropyridine (MPTP) for recreational purposes. MPTP is converted in the body to methylphenyl pyridinium (MPP), which causes selective degeneration of the dopaminergic nigrostriatal system involved in the genesis of the motor deficits of parkinsonism. MPP structurally resembles paraquat, a herbicide. New models of selective nigrostriatal damage, such as neurotoxicity induced by the pesticides rotenone and paraquat, indicate that these environmental agents may indeed contribute to the neurodegenerative process in parkinsonism. Mitochondrial complex I activity is reduced in Parkinson disease; MPP inhibits mitochondrial complex I, as does rotenone. Epidemiologic studies have found an association of Parkinson disease with pesticide exposure, depending on duration of exposure. Petrovitch and colleagues undertook a prospective cohort study with 30-year follow-up of Hawaiian plantation workers, and found a relative risk of Parkinson disease of 1.0, 1.7, and 1.9 for those who had worked on the plantation for 1 to 10, 11 to 20, and more than 20 years, respectively, compared to those who had never done plantation work.[13] Participants were exposed to pesticides but also to many other substances, and the findings from this study cannot determine which exposures influenced the development of parkinsonism. In Taiwan, a history of rural living, farming, use of herbicides/pesticides, and use of paraquat were associated with an increased risk of parkinsonism in a dose–response manner. After adjustment for multiple risk factors, the relationship between Parkinson disease and previous use of herbicides/pesticides and paraquat remained significant, the risk being greater among subjects who had used paraquat plus other herbicides/pesticides rather than in those who had not used paraquat.[14] The risk of developing Parkinson disease was increased more than six times in those exposed for more than 20 years to paraquat.[14]

At the present time, then, it seems that exposure to certain pesticides or herbicides increases the risk of developing Parkinson disease, including pyrethroids, organochlorines, and organophosphates, and 2,4-dichlorophenoxyacetic acid (2,4-D), a constituent of Agent Orange. The precise mechanisms and pesticides or herbicides involved are not known and probably vary depending on genetic and other factors. By assessing lifetime use of pesticides selected by mechanism in a case-control study, however, Parkinson disease has been associated with use of pesticides that inhibit mitochondrial complex I, including rotenone, and with use of pesticides causing oxidative stress, including paraquat.[15]

CONCLUDING COMMENTS

Most physicians have only limited experience of occupationally related neurotoxic disorders, even though the majority of patients with such disorders come under the care of neurologists, primary care physicians, or internists, at least at some point during the course of their disorder. It is therefore important that physicians become and remain sensitive to the possibility that their patients may have diseases induced by toxic exposures occurring at work. Unfortunately, there remains a shortage of physicians with expertise in occupational medicine who can act as clinical or educational resources, and this shortage has proved difficult to remedy. The emphasis has moved to the prevention of occupationally related disorders. In the United States, federal and state legislation regulates and enforces comprehensive safety and health programs in the workplace and also provides for various informational and educational services to improve occupational safety. Nevertheless, physicians must be aware of the basic principles of occupational medicine and understand how to screen for possible neurotoxic disorders, as well as the limitations of the screening process. They must also know the implications of making such diagnoses, understand their responsibilities within the framework of any local or national workers' compensation system, and be aware of any requirements to alert health or regulatory agencies to suspected occupationally related neurotoxic disorders.

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CHAPTER

36

Abnormalities of Thermal Regulation and the Nervous System

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THERMOREGULATORY SYSTEM
CAUSES OF ABNORMAL THERMOREGULATION
  Neurologic Causes of Abnormal Thermoregulation
    Hypothalamic Lesions
    Lesions of Effector Pathways
    Miscellaneous Lesions
    Thermoregulatory System Overload
  Environmental Causes of Abnormal Thermoregulation
    Hyperthermia
    Hypothermia
EFFECTS OF TEMPERATURE ON THE NERVOUS SYSTEM
MANIFESTATIONS AND MANAGEMENT OF ABNORMAL THERMOREGULATION
  Hyperthermia
    Neurologic Manifestations
    Systemic Manifestations
    Patient Management
  Hypothermia
    Neurologic Manifestations
    Systemic Manifestations
    Patient Management
THERAPEUTIC HYPOTHERMIA

THERMOREGULATORY SYSTEM

Mammals maintain their core body temperature within a narrow range despite exposure to a broad range of environmental temperatures. This thermoregulation is achieved by activating a set of thermoeffector systems that generate or dissipate heat, as necessary.[1–4] Basal metabolic activity produces heat, and within a narrow range of ambient temperatures called the thermoneutral zone the core temperature can be maintained by adjusting the metabolic rate. Outside this range, heat generation is achieved primarily by shivering. Newborn infants do not shiver, and shivering is probably not fully effective until several years of age; before then, nonshivering thermogenesis occurs in brown adipose tissue. The mitochondria of brown adipose tissue contain an uncoupling protein that, when induced, diverts the energy generated by oxidative phosphorylation into heat production rather than adenosine triphosphate synthesis, so that heat becomes the primary product of metabolism rather than a byproduct as in other tissues. Piloerection (goosebumps), cutaneous vasoconstriction, and behavioral adaptations (such as postural changes or dressing for the cold) are additional mechanisms of nonshivering thermogenesis.

Heat dissipation is achieved by evaporation (sweating) and by nonevaporative heat loss (conduction, convection, and radiation). Evaporative heat loss is the most important of these mechanisms in most clinical situations. Nonevaporative heat loss can occur only when the ambient temperature is lower than the skin temperature, and the amount of heat it dissipates is a function of vasomotor activity; increased skin blood flow promotes heat dissipation, and reduced skin blood flow minimizes it.

The activity in each of these thermoeffector systems is a function of thermal input from spatially distributed thermoreceptors providing information about body temperature, both in the core (the brain and viscera of the thorax and abdomen) and in the shell (peripheral tissues, primarily skin). Most of the research regarding peripheral sensation of non-noxious thermal stimuli has focused on skin thermosensors. In humans, fibers activated by cold are rapidly adapting A-delta fibers, and fibers activated by warm temperatures are primarily C-fibers.[1–3,5] Their temperature sensitivity is probably mediated by transient receptor potential channels, a family of cation channels expressed in cell membranes. Nine members of this family are sensitive to temperature, with relatively narrow—but overlapping—ranges

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of temperature sensitivity. In addition to skin thermosensors, the afferent limb of the thermoregulatory system includes visceral thermosensors, vascular thermosensors, and neurons within the hypothalamic regulatory areas that are sensitive to the temperature in the hypothalamus itself. Thermosensitive neurons are also present in the brainstem and spinal cord and, possibly, in the abdominal viscera.

The preoptic anterior hypothalamus is the principal site at which the afferent thermal input is integrated and the thermoeffector systems are activated. The specific function determining effector activity in response to a given thermal input is different for each thermoeffector system. The combined activity of all the thermoeffector systems results in a body temperature at which heat gain matches heat loss, referred to as the balance point, or equilibrium point.[1–3] Thermoregulatory disorders occur when thermal afferent pathways or thermoeffector systems malfunction or environmental conditions overwhelm their capacity.[6] Fever is caused by altering the functions relating thermoeffector activity to thermal afferent input, resulting in a shift of the thermoregulatory balance point.

CAUSES OF ABNORMAL THERMOREGULATION

Most thermoregulatory disorders are caused by environmental conditions that overwhelm the body's thermoeffector systems, but some are caused by neurologic disorders that disrupt thermoregulatory function. The main neurologic causes of abnormal thermoregulation are diseases of the hypothalamus or its autonomic outflow. In addition, a few neurologic disorders result in excessive heat production that overwhelms the thermoregulatory system. Tables 36-1 and 36-2 summarize the main causes of hyperthermia and hypothermia.[6–8]

Neurologic Causes of Abnormal Thermoregulation

HYPOTHALAMIC LESIONS

Hypothalamic lesions may produce either hyperthermia or hypothermia, although hypothermia is more common. Hyperthermia has been described with tumors, stroke, encephalitis, trauma, and surgery. Hypothermia has been reported with tumors, stroke, subarachnoid hemorrhage, sarcoidosis, multiple sclerosis, neuromyelitis optica, limbic encephalitis, Parkinson disease, and idiopathic gliosis. Hypothermia is common in Wernicke encephalopathy and may be the presenting feature. In contrast, although fever occurs in about 12 percent of patients with Wernicke encephalopathy, a superimposed infection is almost always responsible. Prominent abnormalities of sweating (anhidrosis or hypohidrosis) have been described in primary autonomic failure,

TABLE 36-1 ■ Causes of Hyperthermia

Malfunction of Thermoregulatory System

- Hypothalamic disorders
  - Tumor
  - Stroke
  - Encephalitis
  - Head trauma
  - Surgery
- Other lesions
  - Hydrocephalus
  - Posterior fossa surgery

Interruption of Effector Pathways

- Spinal cord lesions
- Autonomic neuropathies

Overwhelming Heat Production or Exposure

- Neurologic conditions
  - Status epilepticus
  - Delirium tremens
  - Tetanus
  - Malignant hyperthermia
  - Neuroleptic malignant syndrome
  - Serotonin syndrome
- Non-neurologic conditions
  - Heat stress disorders (exertional or nonexertional)
    - Heat shock
    - Heat exhaustion
  - Endocrine disorders
    - Thyrotoxicosis
    - Pheochromocytoma
  - Drugs

Inadequate Heat Dissipation

- Dehydration
- Skin disorders
- Occlusive dressings
- Drugs

TABLE 36-2 ■ Causes of Hypothermia

Malfunction of Thermoregulatory System

- Hypothalamic disorders
  - Tumor
  - Stroke
  - Subarachnoid hemorrhage
  - Sarcoidosis
  - Wernicke encephalopathy
  - Parkinson disease
  - Primary autonomic failure
  - Multiple system atrophy
  - Multiple sclerosis
- Agenesis of the corpus callosum (Shapiro syndrome)
- Disease at the mesencephalic-diencephalic junction

Interruption of Effector Pathways

- Spinal cord lesions
- Autonomic neuropathies
- Neuromuscular causes of weakness

Inadequate Heat Production

- Accidental hypothermia (exposure)
- Endocrine disorders
  - Hypothyroidism
  - Hypoadrenalism
  - Hypopituitarism
- Derangements of glucose regulation
  - Hypoglycemia
  - Diabetic ketoacidosis
  - Hyperosmolar coma
- Malnutrition
- Drugs

Excessive Heat Dissipation

- Severe burns
- Skin disorders (exfoliative dermatitis, psoriasis, ichthyosis, erythroderma)

multiple system atrophy, and as an isolated condition, and hyperthermia may develop when these patients are exposed to hot climates without air conditioning.[8]

LESIONS OF EFFECTOR PATHWAYS

Interruption of the autonomic outflow from the hypothalamus may produce either hyperthermia or hypothermia by impairing the effector mechanisms necessary for heat dissipation or production, respectively. Lesions of the spinal cord above the thoracic level may interrupt descending input to the thoracic intermediolateral cell column, producing both vasomotor abnormalities and disorders of sweating, or to anterior horn cells, impairing or eliminating shivering below the level of the lesion.

Any neuromuscular disease that is severe enough to cause profound weakness can impede shivering. Polyneuropathies that involve autonomic fibers can produce abnormalities of vasomotor activity and sweating, and either hypothermia or hyperthermia may result.[7,8] For example, hypothermia is common in patients with diabetes, probably because of impaired vasomotor reflexes. In contrast, some patients with diabetes manifest a syndrome of heat intolerance that is attributed to anhidrosis. Because the autonomic nerve involvement in diabetes is usually predominantly distal, these patients sometimes exhibit profuse sweating over the head and upper trunk ("compensatory hyperhidrosis").

MISCELLANEOUS LESIONS

Disorders that produce widespread damage to the central nervous system (CNS) can impair thermoregulation, but the precise mechanism is often difficult to establish. Degenerative diseases can be associated with hypothermia, possibly because of impaired behavioral adaptations to cold. Hyperthermia has been reported in patients with acute hydrocephalus, posterior fossa surgery, ischemic strokes, and intracranial hemorrhage, but as a general rule, hyperthermia should not be attributed to "neurogenic factors" even when a patient has CNS disease unless there is clear involvement of the hypothalamus or its effector pathways and other causes of fever have been excluded.[9]

Agenesis or dysplasia of the corpus callosum may be associated with episodic hyperhidrosis and hypothermia (Shapiro syndrome).[6,10] There may also be associated structural abnormalities in the septal region, cingulate gyrus, and posterior hypothalamus. The periods of sweating may last from minutes to hours, and the hypothermia may last from 30 minutes up to several weeks. Episodes may be separated by intervals of months to years. There is often ataxia and impaired cognition during the hypothermic episodes. A similar syndrome has occasionally been seen without any associated abnormality of the corpus callosum, and neurotransmitter abnormalities have been identified in some cases. Episodic hypothermia without hyperhidrosis has also been described. Recurrent hypothermia has also been attributed to "diencephalic epilepsy," but electrographic seizures have not been demonstrated consistently.

Cases of periodic hyperthermia associated with agenesis of the corpus callosum ("reverse Shapiro syndrome") have been reported. Episodic hyperthermia (or hypothermia) associated with other manifestations of autonomic dysfunction has also been described after head trauma and many other neurologic disorders.

THERMOREGULATORY SYSTEM OVERLOAD

Several neurologic diseases produce thermoregulatory disorders by creating conditions that overwhelm the capacity of the thermoregulatory system. Just as paralysis may eliminate effective shivering and result in hypothermia, muscle hyperactivity may result in hyperthermia. Elevated body temperatures are common after generalized seizures, tetanus, and delirium tremens, for example. Three important examples of hyperthermia associated with increased muscle activity are malignant hyperthermia, neuroleptic malignant syndrome, and serotonin syndrome.

Malignant hyperthermia is characterized by vigorous muscle contractions and an abrupt increase in temperature on exposure to certain drugs, most commonly inhalational anesthetics and succinylcholine.[11] It can occur at any time during anesthesia administration or shortly thereafter. The hyperthermia is probably a direct result of the heat produced by sustained muscle activity resulting from defective regulation of intracellular free calcium. Malignant hyperthermia is inherited as an autosomal dominant trait with variable penetrance, and a predominance of expression in young males. More than 50 percent of patients have mutations in the gene for the ryanodine receptor, the primary channel for release of calcium stored in the sarcoplasmic reticulum; other cases are due to mutations in the gene encoding the main subunit of the dihydropyridine receptor, a voltage sensor that interacts closely with the ryanodine receptor, or in the gene coding for Stac3 protein, which is thought to be important for effective co-location of dihydropyridine receptors and ryanodine receptors. Mutations in the gene for the ryanodine receptor have also been implicated in several congenital myopathies including central core disease, centronuclear myopathy, multiminicore disease, congenital fiber-type disproportion, and nemaline rod myopathy; some, but not all, patients with these conditions are also at risk of malignant hyperthermia. Although patients with other myopathies, muscular dystrophies, and myotonia may have adverse effects from anesthesia (e.g., contractures after administration of succinylcholine, increased susceptibility to respiratory depression after receiving barbiturates or opiates, disease-related cardiac complications, or rhabdomyolysis), they do not appear to have an increased risk of malignant hyperthermia.

Both *neuroleptic malignant syndrome* and *serotonin syndrome* are characterized by hyperthermia, diaphoresis, rigidity, mental status changes, tachypnea, tachycardia, and hypertension or labile blood pressure.[12] Patients with neuroleptic malignant syndrome typically have hyporeflexia, normal pupillary responses, and normal or decreased bowel sounds, whereas serotonin syndrome is associated with hyperreflexia, dilated pupils, and hyperactive bowel sounds. Patients with neuroleptic malignant syndrome often have laboratory abnormalities that are not present in serotonin syndrome, including peripheral leukocytosis, elevated serum creatine kinase, increased liver enzymes, and low serum iron, magnesium, and calcium levels. The pathophysiology of these two syndromes is poorly understood. The elevated body temperatures are at least partly due to increased muscle activity, but increased sympathetic activity and increased levels of acute-phase reactants probably contribute to the hyperthermia of neuroleptic malignant syndrome, and nonshivering thermogenesis in brown adipose tissue and cutaneous vasoconstriction may contribute to the hyperthermia of serotonin syndrome. Neuroleptic malignant syndrome is typically triggered by exposure to neuroleptic agents, including atypical antipsychotic agents, but it has also been described in patients being treated for presumed Parkinson disease after sudden withdrawal of dopaminergic agents or changes in their medication regimen (sometimes referred to as parkinsonism hyperpyrexia). When associated with neuroleptics, the condition typically arises within 2 weeks of starting therapy or increasing the dose, but at times it may begin within hours or after a delay of months. Serotonin syndrome can occur with any serotonergic drugs—notably tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and meperidine—especially when used in combination.

Environmental Causes of Abnormal Thermoregulation

Most cases of abnormal thermoregulation occur in individuals without a primary neurologic disease and are caused by external temperature conditions (or, less commonly, internal metabolic derangements) that overwhelm the thermoregulatory system.

HYPERTHERMIA

Conditions in which the thermoregulatory system is overwhelmed by extremely high external temperatures are called *heat stress disorders*. The most severe form is heat stroke, defined as a core body temperature exceeding 40°C (or 41°C according to older sources) associated with CNS dysfunction such as delirium, seizures, or coma.[6,13,14] Heat stroke is characterized by hot, dry skin, but this is not used as a diagnostic criterion. Heat exhaustion is a milder form, characterized by progressive lethargy, headache, vomiting, tachycardia, and hypotension, with less severe neurologic impairment than occurs in heat stroke. These two conditions form a continuum: if untreated, heat exhaustion may progress to heat stroke.

Classic heat stroke results from prolonged exposure to high environmental temperatures while the individual undertakes normal activities; exertional heat stroke occurs in situations of physical exertion, typically in healthy young individuals, often athletes or military personnel. Inadequate cardiovascular conditioning, poor acclimatization, dehydration, heavy clothing, low work efficiency, and reduced ratio of skin area to body mass all are risk factors. Congenital or acquired abnormalities of sweat gland function may contribute. Classic heat stroke is typically seen in the elderly, especially in those with chronic diseases (e.g., alcoholism, malnutrition, diabetes, cardiovascular dysfunction, obesity), but prepubertal children are also at risk. Some medications predispose to the condition, including anticholinergics, β-blockers, diuretics, antihistamines, antidepressants, and amphetamines. People in lower socioeconomic groups are at particular risk, especially those living in urban areas, because they may be exposed to a greater thermal load and live in apartments with inadequate ventilation.

The most common cause of hyperthermia is simple dehydration because it results in vasoconstriction and decreased sweating, interfering with heat dissipation. Heat dissipation may also be impaired in advanced scleroderma or in miliaria, or by extensive use of occlusive dressings. Both thyrotoxicosis (mainly during thyroid storm) and pheochromocytoma may cause hyperthermia on the basis of hypermetabolism. Drug exposure can also produce hyperthermia in several ways, including increased metabolic rate, hyperactivity, and impaired heat dissipation (Table 36-3).

HYPOTHERMIA

As with hyperthermia, hypothermia is usually due to conditions that overwhelm the thermoregulatory system, rather than a consequence of primary malfunction in the system.[6,14,15] Accidental hypothermia is defined as an unintentional decline in the core temperature below 35°C. It is most common in neonates, the elderly, and those who are unconscious or immobile, especially from drug exposure. Alcohol, in particular, is a vasodilator, a CNS depressant, an anesthetic, and a risk factor for trauma and environmental exposure, all of which increase the risk of hypothermia. Other drugs predispose to hypothermia through a variety of mechanisms including depression of the hypothalamic center, inhibition of shivering by neuromuscular blockade, and vasodilation (Table 36-4).

Patients with severe burns, exfoliative dermatitis, or other dermatologic conditions may develop hypothermia because of increased evaporative and nonevaporative heat loss and the inability to regulate these processes through vasoconstriction. Hypothermia may also occur in the setting of several endocrine disorders that impair metabolism including hypothyroidism, hypoadrenalism, and hypopituitarism. Hypoglycemia, diabetic ketoacidosis, and hyperosmolar coma are also associated with hypothermia, but it is not clear whether this is because of a hypometabolic state or a direct effect on the hypothalamus.

EFFECTS OF TEMPERATURE ON THE NERVOUS SYSTEM

Neuronal function is significantly affected by even moderate changes in temperature.[16] Basic electrical parameters (such as membrane capacitance, axoplasmic resistance, maximal sodium and potassium conductances, and ion channel rate constants) vary systematically with temperature. Consequently, temperature affects the action potential amplitude, duration, maximal rate of rise, net ionic movements, and conduction velocity, and therefore changes the likelihood of signal propagation or conduction block. Clinical electrophysiologic tests reflect these effects; for example, the maximal motor conduction velocity of the ulnar nerve falls by 2.4 m/sec for every 1°C decline in temperature. As the temperature declines, compound action potential

TABLE 36-3 ■ Pharmacologic Agents that Promote Hyperthermia

Agent	Excess Heat Production		Impaired Heat Dissipation		Other Mechanisms
	Occurrence	Cause or Comment	Occurrence	Caus	
Anticholinergic agents			+		
Vasoconstricting agents			+		
β-Blockers			+		
Diuretics			+		
Antihistamines			+		
Barbiturates			+		
Alcohol			+		
Topiramate			+	Hypohidrosis	
Zonisamide			+	Hypohidrosis	
Tricyclic antidepressants	+	Increased motor activity	+	Anticholinergic effects	
Cocaine	+				
Amphetamines	+				
Opiates	+				
Lysergic acid diethylamide (LSD)	+				
Cannabinoids	+				
Phenothiazines	+	Neuroleptic malignant syndrome	+	Anticholinergic effects	Possible effect on hypothalamus
Butyrophenones	+	Neuroleptic malignant syndrome			Failure to recognize thirst, possible effect on hypothalamus
Atypical antipsychotics	+	Neuroleptic malignant syndrome			
Salicylate overdose	+				
Anticholinesterase agents					Cause unknown
Methyldopa					Idiosyncratic
Propylthiouracil					Idiosyncratic
Inhalational anesthetics	+	Malignant hyperthermia			
Monoamine oxidase inhibitors (overdose in conjunction with meperidine or biogenic amine precursors)	+	Serotonin syndrome			
Serotonin reuptake inhibitors	+	Serotonin syndrome			
Triptans (in conjunction with SSRIs or SNRIs)	+	Serotonin syndrome			

SNRI, Serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

TABLE 36-4 ■ Pharmacologic Agents that Promote Hypothermia

Agent	Impaired Heat Production	Excessive Heat Loss	Other Mechanisms
Alcohol	+	+	Possible effect on hypothalamus
Barbiturates	+		
General anesthetics	+		
Neuromuscular blocking agents	+		
Phenothiazines	+	+	
Benzodiazepines	+		
Tricyclic antidepressants		+*	
Vasodilating agents		+	
Bromocriptine			Possible effect on hypothalamus
Reserpine			Possible effect on hypothalamus
Acetaminophen			Possible effect on hypothalamus
Lithium			Possible effect on hypothalamus
Valproic acid			Mechanism unknown
Penicillin			Mechanism unknown
Erythromycin			Mechanism unknown

*Hyperhidrosis in some subjects.

amplitudes increase, the duration of motor unit action potentials increases, mean amplitude declines, and polyphasic potentials become more frequent. Hypothermia also prolongs the latencies of visual, somatosensory, and brainstem auditory evoked potentials.[15]

Although these alterations in function can have clinical consequences, actual nervous system injury does not occur until extreme temperatures are reached. Direct thermal injury to the brain and spinal cord results in the production of a variety of cytokines and altered expression of heat-shock proteins, leading to excitotoxicity, endothelial cell injury, breakdown of the blood–brain barrier, and diffuse microvascular thrombosis, ultimately causing cell death, edema, and hemorrhage.[6,16,17]

Cerebral metabolic rate and oxygen metabolism increase with rising temperatures between 38° and 42°C, but decline as temperatures rise further. Hypothermia leads to slowing of the rate of chemical reactions, decrease in the metabolic requirement for oxygen, and reduction of cerebral blood flow by 4.4 to 6.0 percent for every 1°C decline in temperature.[15] This reduction in metabolic rate is protective, but neural damage still occurs. It is difficult to know to what extent the neuronal damage is a direct effect of low temperatures rather than a consequence of secondary injury from the systemic effects of hypothermia (including cardiovascular collapse).

MANIFESTATIONS AND MANAGEMENT OF ABNORMAL THERMOREGULATION

Hyperthermia

Neurologic Manifestations

The earliest neurologic manifestations of hyperthermia include thirst, weakness, and fatigue. Skeletal muscle cramps may occur in the exertional heat stress disorders and are probably related to hyponatremia and increased intracellular calcium release. Patients with heat exhaustion are frequently agitated and may develop delirium and incoordination. Tetany or paresthesias sometimes will occur secondary to hyperventilation.

Heat stroke may present with the sudden onset of stupor or coma, or patients may pass through a prodromal period that can include progressive headache, drowsiness, confusion, agitation, and delirium.[6,14,17] Seizures occur in 60 to 70 percent of patients. Pupils are usually small and often pinpoint, and vestibulo-ocular ("cold caloric") responses are intact except terminally. Diffuse hypertonia is common, but flaccidity has also been described. Hemiplegia, cerebellar deficits, and papilledema may also occur. Cerebrospinal fluid (CSF) from patients with heat stroke is usually normal but may show an increased protein concentration, xanthochromia, or mild lymphocytic pleocytosis. Slowing of the electroencephalogram (EEG) occurs at temperatures above 42°C.

Most patients who recover from heat stroke have no permanent neurologic sequelae, but some may have persistent ataxia and dysarthria; a few cases of hemiparesis, myelopathy, or quadriparesis have been reported. There are also reports of persistent polyneuropathy after patients have been treated with experimental whole-body hyperthermia for cancer, and localized neuropathies following hyperthermic isolated limb perfusion. Survivors of severe heat stroke may also develop premature cataracts, attributed to dehydration.

SYSTEMIC MANIFESTATIONS

Heat stroke is associated with diffuse systemic derangements.[6,13] The mildest are dependent edema and syncope. Respiratory alkalosis is almost always present, and tetany may occur. Hypoxia, metabolic acidosis, hypokalemia, hyperkalemia, hypernatremia, hypophosphatemia, hypomagnesemia, and hypoglycemia have each been described. Peripheral leukocytosis in the range of 20,000 to 30,000 cells/mm^3 is common.

Cardiovascular manifestations include low cardiac output and low diastolic pressure. Subendocardial hemorrhages may occur. Minor electrocardiographic changes are sometimes found and include transient conduction abnormalities and inverted or flattened T waves. Apart from the respiratory alkalosis, pulmonary manifestations may include pulmonary edema and acute lung injury in the presence of disseminated intravascular coagulation.

Rhabdomyolysis is almost universal in exertional heat stroke but is uncommon in classic heat stroke. Elevated serum creatine kinase levels occur in both conditions, often followed by elevated levels of lactate dehydrogenase. Acute renal failure occurs in about 25 percent of patients with exertional heat stroke but is uncommon in classic heat stroke. Diarrhea and vomiting are common; melena and hematemesis may occur in severe cases. Elevated serum amylase and liver enzymes are common; liver injury is usually asymptomatic, but acute liver failure occurs in 5 percent of patients with exertional heat stroke. Clinically significant coagulopathies are common and, in severe heat stroke, disseminated intravascular coagulation is almost always present.

PATIENT MANAGEMENT

There are three components to the management of the hyperthermic patient: treatment of the underlying cause (when possible), cooling, and treatment or prevention of common complications.[6,13,14]

Most of the hypothalamic causes of hyperthermia are not amenable to acute treatment, although corticosteroid administration is appropriate when there is vasogenic edema. Compressive spinal cord lesions associated with hyperthermia (e.g., epidural hematoma or abscess) may require immediate treatment, but no acute treatment is possible for most other lesions. Hyperthermia caused by excessive muscle activity (including status epilepticus) is treated by reducing or eliminating the muscle activity.

Patients with malignant hyperthermia are treated by stopping the responsible anesthesia, placing activated charcoal filters, instituting hyperoxygenation, and intravenously administering dantrolene, a skeletal muscle relaxant that uncouples excitation and contraction by preventing the release of calcium from the sarcoplasmic reticulum.[11] Although dantrolene has been used successfully to treat neuroleptic malignant syndrome, bromocriptine and amantadine have also been tried in some cases, probably because of the apparent role of dopaminergic systems in neuroleptic malignant syndrome. Electroconvulsive therapy may be useful in severe, refractory cases. Cyproheptadine is the most commonly recommended medication for serotonin syndrome, but it has not been studied rigorously.[12]

Non-neurologic causes of hyperthermia may also be amenable to specific treatment. Thyrotoxic storm or crisis is treated with β-adrenergic antagonists, glucocorticoids (because of increased requirement and reduced adrenal reserve), and administration of an antithyroid agent. Patients with pheochromocytoma are treated with α-adrenergic antagonists. Dehydrated patients are rehydrated as necessary. For hyperthermic patients in whom a precipitating drug can be identified, treatment is directed at minimizing the drug's toxicity. Patients with alcohol withdrawal and delirium tremens require large doses of benzodiazepines. For the hyperthermia of heat stress disorders, treatment of the underlying cause simply consists of removing the patient from the hot environment and cooling the patient.

Cooling may be achieved by either evaporative or direct external methods.[6,13] Centrally acting antipyretic medications affect the thermoregulatory balance point, so they are appropriate for use in fever, where the balance point is abnormally high, but not in heat stroke or heat exhaustion. Evaporative cooling methods involve wetting the skin with tepid water and directing bedside fans at the patient. Direct external cooling involves immersion of the patient in ice water, use of a hypothermic mattress, or packing the patient in ice. These direct external cooling techniques produce vasoconstriction, which impedes removal of heat from the core; therefore, in order to counteract this response, these cooling methods are applied (either simultaneously or in alternation) with vigorous skin massage, tepid (40°C) water spray, or exposure to hot moving air (45°C). Cooling is more rapid and more effective with direct external methods than with evaporative methods, but evaporative techniques are often adequate and permit easier patient management and monitoring. In rare instances where neither method is sufficient, more aggressive options include peritoneal lavage with iced saline, gastric lavage or enemas with ice water, and hemodialysis or cardiopulmonary bypass with external cooling of blood.

Regardless of the cooling method used, shivering often occurs as the body temperature falls and hampers cooling. In the case of cold water immersion, the rate of heat transfer is high enough that the heat produced by shivering is generally not a concern. If necessary, shivering can be treated with phenothiazines, benzodiazepines, meperidine, or nondepolarizing muscle relaxants; serotonin uptake inhibitors, α_2 agonists, and *N*-methyl-D-aspartate antagonists have also been proposed. As the patient's core temperature reaches 38° or 39°C, cooling should be stopped to avoid overshoot hypothermia.

The most important complication of hyperthermia is hypotension, which should be treated with fluid administration. Vasopressors may be used if necessary, but those that produce vasoconstriction should be avoided. Patients should receive 100 percent oxygen until adequate oxygenation is documented. Serum electrolyte and glucose concentrations should be assessed frequently and treated as necessary. To promote urine output, patients are often given an initial dose of mannitol or furosemide and subsequent doses of diuretics as necessary. If seizures occur they should be treated with benzodiazepines. Disseminated intravascular coagulation should also be treated if it occurs. Appropriate treatment of heat stroke results in a 90 to 95 percent survival rate. Poor prognosis is associated with a peak temperature higher than 41°C, prolonged symptoms before initiation of treatment, acute renal failure, elevated serum liver enzymes, red blood cell apoptosis on early peripheral blood smears, and persistence of coma after restoration of normothermia.

Hypothermia

NEUROLOGIC MANIFESTATIONS

The neurologic manifestations of hypothermia progress in a relatively predictable manner.[6,14,15] Thought processes may be normal with rectal temperatures as low as 34°C, but below this temperature most patients exhibit psychomotor slowing, speech perseveration, lethargy, or confusion. A few patients have been described as alert with rectal temperatures as low as 31°C, but this is uncommon. Dysarthria develops at temperatures below 33.5°C, and below 28°C most patients only grunt in response to questions, although some patients remain verbally responsive at temperatures as low as 23.5°C. Most patients still make purposeful responses to noxious stimuli even with temperatures approaching 20°C.

Pupillary reaction to light becomes progressively more sluggish as temperatures decline below about 32°C, but pupillary size and eye movements do not correlate reliably with temperature. Deep tendon reflexes are typically normal or even increased at temperatures as low as 29.5°C, but they become progressively diminished at lower temperatures. Extensor plantar responses are rare at any level of hypothermia. Increased muscle tone is frequent even in mild hypothermia, and it is universal at temperatures below 29.5°C. Myotonia is a common finding. Focal dystonias and dyskinesias are rare, but patients may exhibit a characteristic posture consisting of flexion in all four limbs.

No specific CSF abnormalities have been described in hypothermia. The EEG frequency spectrum changes, with increased beta and theta activity and reduced alpha activity. At temperatures below 28°C, there is progressive slowing. As the temperature declines further, a burst-suppression pattern appears, with the EEG becoming isoelectric below 10° to 20°C. Brainstem auditory evoked potentials show increasing latencies of waves I, III, and V as temperature decreases. Visual evoked potential latencies also increase progressively as temperature declines. The changes that occur in electromyographic and nerve conduction studies were discussed earlier.

Patients who recover from hypothermia usually have no long-term neurologic problems.

SYSTEMIC MANIFESTATIONS

During the shivering phase (typically between 35° and 30°C), there is an initial rise in metabolic rate and oxygen consumption, with corresponding increases in respiratory rate, heart rate, and blood pressure, but at temperatures below about 30°C shivering ceases and there is a rapid decline in metabolic rate and oxygen consumption—respiration slows and becomes shallow, the heart rate decreases, and cardiac output declines.[6,15] Clinically significant hypotension typically does not occur until temperatures of 25°C and below are reached. The principal cardiac concern with hypothermia is arrhythmia. Arrhythmia is preceded by the characteristic J-point elevation (or

"Osborn wave") that appears in the electrocardiogram at about 33°C and becomes increasingly prominent as the temperature declines. Atrial fibrillation is common below 33°C, but all types of atrial and ventricular arrhythmias can occur.

Mild hypothermia induces diuresis because peripheral vasoconstriction redistributes blood to internal organs including the kidneys, and also because of inhibition of antidiuretic hormone release and decreased renal tubular function. As hypothermia progresses and cardiac output diminishes, renal blood flow and glomerular filtration rate decline, ultimately resulting in acute renal failure. Hemoconcentration increases the hematocrit by 2 percent for every 1°C drop in core temperature. With falling temperatures, the platelet count progressively declines due to bone marrow suppression and splenic or hepatic sequestration. Platelet function is also impaired. Cold suppresses the enzymatic function of activated clotting factors, leading to coagulopathies that may not be detected on standard laboratory tests which are performed at 37°C. Hypercoagulability can also develop due to thromboplastin release from cold tissue, catecholamine and steroid release, and circulatory collapse. Granulocytopenia may occur with temperatures below 28°C.

Hypothermia has no consistent effect on potassium, calcium, magnesium, or other electrolytes, but moderate hypoglycemia is common. Endocrine functions generally remain normal. Ileus is frequent, and ischemic pancreatitis can also occur; serum amylase levels appear to correlate with the severity of hypothermia. Depressed airway reflexes result in a high incidence of pneumonia.

PATIENT MANAGEMENT

The management of hypothermia is analogous to the management of hyperthermia. The three principal components are treatment of the underlying cause (when possible), rewarming, and treatment or prevention of common complications.[6,14,15]

Treatment of hypothalamic and spinal cord pathology causing hypothermia is similar to that discussed for hyperthermia. In addition, thiamine should be given routinely to hypothermic patients unless Wernicke encephalopathy has been excluded. Spells of episodic hyperhidrosis and hypothermia have responded to cyproheptadine, clonidine, β-blockers, anticonvulsants, dopamine agonists, or peripheral muscarinic blockade with oxybutynin or glycopyrrolate.

Any metabolic derangement predisposing to hypothermia should be corrected. For example, exogenous thyroxine is usually required to treat myxedema coma. Patients should be evaluated for trauma and drug or toxin ingestion. For patients with dermatologic conditions and those without any predisposition to hypothermia other than environmental exposure, treatment of the underlying cause consists of drying the patient and removal from the cold environment.

There are three rewarming methods: passive external rewarming, active external rewarming, and active core rewarming.[6,14,15] Passive external rewarming is the slowest and least invasive of these techniques: patients are placed in a warm environment and covered with blankets or aluminized body covers, and intravenous fluids are warmed to a temperature of 36° to 39°C. This technique is usually adequate for patients with a core temperature of 32°C or above as long as the external hypothermic stresses are removed; patients who must avoid the cardiovascular stress of shivering may require active rewarming unless the shivering can be suppressed with benzodiazepines or meperidine or eliminated through neuromuscular blockade (in patients who are already sedated and receiving mechanical ventilation).

Active external rewarming consists of heating the skin with heating pads, heated blankets, hot water bottles, or a forced air heating system; radiant heat from a light source; or immersion in warm water. Concerns include the risk of burn injuries to the vasoconstricted skin and the possibility of "core temperature after-drop" because warming the skin prior to the core may result in peripheral vasodilatation and enhance return of cold, acidic blood to the core.

Active core rewarming techniques include the administration of heated oxygen by face mask or endotracheal tube, warmed intravenous fluids, warm gastric or bladder irrigation, warm lavage (peritoneal, thoracic, mediastinal, or colonic), and cardiopulmonary bypass or extracorporeal membrane oxygenation. The optimal rewarming rate is unknown, and the relative efficacy of these methods has not been established. Extracorporeal rewarming is preferred in patients with circulatory arrest.

All hypothermic patients with a severely depressed level of consciousness should be intubated to prevent aspiration. Patients should receive 100 percent oxygen until adequate oxygenation has been documented. Blood gas interpretation is complicated in the setting of hypothermia, and the optimal strategy for managing acid–base status remains controversial.

Hypotension in hypothermic patients is generally due to dehydration resulting from increased urine output, and fluid resuscitation is usually adequate. The role of inotropic agents is debated, because they have reduced efficacy at temperatures below 30°C and may be arrhythmogenic. Similarly at temperatures below 30°C, cardiac arrhythmias are resistant to many pharmacologic agents, pacing efforts, and defibrillation. Fortunately, many atrial arrhythmias and transient ventricular arrhythmias convert spontaneously during rewarming. For persistent ventricular arrhythmias, no antiarrhythmic agent has been shown to be safe and effective.

Treatment of hypothermia can lead to changes in serum electrolyte levels, requiring frequent monitoring. Hyperkalemia or hypophosphatemia may be particularly severe. Patients should be assessed for coagulopathy, including disseminated intravascular coagulation. A nasogastric tube should be inserted and serum amylase level checked because of the risk of ileus and pancreatitis.

The prognosis in hypothermia is influenced more by the patient's age and underlying disease than by the magnitude of the temperature decline. Some patients have been successfully resuscitated after 2 hours of apparent arrest, and others have survived temperatures below 20°C. This has prompted some to advocate warming all patients to normal temperatures before concluding that resuscitation is futile ("patients are not dead unless they are warm and dead").

THERAPEUTIC HYPOTHERMIA

A 12- to 24-hour period of therapeutic hypothermia to a target of 32° to 34°C is recommended for unconscious adults who have achieved return of spontaneous circulation after out-of-hospital cardiac arrest when the initial rhythm was ventricular fibrillation or pulseless ventricular tachycardia, based on studies showing reduced mortality and improved neurologic outcome.[18] Further investigation is required to determine the optimal duration of treatment, target temperature, and cooling method, as well as the efficacy of hypothermia when cardiac arrest occurs in the hospital or after other rhythms. Therapeutic hypothermia has not been demonstrated to improve outcomes after head trauma or other neurologic injury, or during neurosurgical procedures. Clinicians assessing prognosis in patients who are comatose following cardiac arrest need to recognize that predictive clinical findings and laboratory tests may be less reliable following therapeutic hypothermia.[19] Even the criteria for brain death in this setting may need to be revisited.

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CHAPTER

37

Concussion

CATHRA HALABI

DEFINITIONS AND EPIDEMIOLOGY
PATHOPHYSIOLOGY AND BIOMARKERS
CLINICAL APPROACH
  Active Recovery
  Concussion Subtypes
SUBSEQUENT DEVELOPMENT OF NEURODEGENERATIVE DISEASE
CONCLUDING COMMENTS

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality worldwide.[1] The vast majority of injuries are classified as “mild” using current diagnostic criteria, and concussion is considered the mildest form of TBI. Concussion and mild TBI (mTBI) are terms that are often used interchangeably, with some controversy.[2] Many position statements and clinical practice guidelines from professional organizations use the term “concussion/mTBI,” and while all concussions are classified under the umbrella of mTBI, all mTBIs are not concussions. When there are intracranial abnormalities on brain imaging, a classification of “complicated mTBI” should be applied rather than concussion and may be associated with worse outcomes.

The term “postconcussion syndrome” has historically been used to describe a persistent constellation of symptoms following concussion/mTBI. However, these long-lasting symptoms may also reflect alternative diagnoses including premorbid medical conditions. The term “persistent postconcussive symptoms” may be preferred, in part to minimize misattribution of symptoms to ongoing or active brain injury,[3] and to minimize maladaptive perspectives toward recovery for both patients and their clinicians. “Subconcussive head trauma” refers to impact without clinical signs or symptoms meeting the threshold for concussion/mTBI diagnosis, though exposure to repeat subconcussive head trauma has been associated with neurodegenerative disease, including chronic traumatic encephalopathy (CTE).

Despite classification as the mildest form of TBI, concussion/mTBI may cause a wide range of debilitating symptoms with related functional impairment spanning the acute and chronic postinjury periods. Early recognition, reassurance, and systematic treatment strategies may improve outcomes and help guide safe return-to-activity parameters. There are numerous position statements and practice guidelines from professional organizations that address the recognition, diagnosis, and management of concussion/mTBI, and these are updated frequently.[4–6] This chapter focuses on the clinical approach to concussion/mTBI in adults and highlights this complex condition as a treatable entity.

DEFINITIONS AND EPIDEMIOLOGY

Concussion/mTBI is a purely clinical diagnosis. Characteristics include a history of altered neurologic function due to an external force transmitted to and through the brain, often leading to transient changes in the level of alertness or orientation. Concussion/mTBI may occur in a diverse range of circumstances. Common examples include blunt nonpenetrating head trauma from community events such as falls or assault, acceleration and deceleration forces from whiplash in traffic collisions, body checking in contact or collision sports, or blast injury among military personnel. Based on clinical features ascertained at

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time of injury (sometimes specified as within 30 minutes from index event), a diagnosis of concussion/mTBI can be distinguished from moderate and severe TBI in several ways using the current system of injury stratification. There is usually a transiently altered level of alertness or orientation, no or only brief (0 to 30 minutes) loss of consciousness, peri- or post-traumatic amnesia lasting less than 24 hours, the onset of neurologic or other symptom immediately or within 1 to 2 days, and a Glasgow Coma Scale (GCS) score of 13 to 15. In 2015, the Department of Defense (DoD) published a memorandum indicating that the GCS should not be used in diagnoses of TBI.

Concussion/mTBI is a global health problem. In the United States alone, there may be at least 2.5 million TBI-related emergency department encounters annually, and this is likely an underestimate due to unrecognized concussive injury, patient or clinician misappropriation of symptoms to alternative diagnoses, or under-reporting.[1] The majority (80 to 90% or more) of all head injuries are classified as concussion/mTBI. Traffic and other community accidents may occur indiscriminately, but there are several groups at particular risk for sustaining head injury, including athletes, older adults (from falls), military personnel, and individuals with a prior history of TBI. Different mechanisms of injury may instigate distinct pathophysiologic sequelae, such as with blast exposure. There may also be unique patient or population level attributes that affect acute and subacute periods (e.g., physical resilience in athletes, cognitive vulnerability in older adults). Nonetheless, current injury classifications and subsequent management strategies are applied broadly to identify and treat concussion/mTBI since there is a paucity of evidence at this time to promote significantly differing management strategies solely based on the mechanism of injury.[6] Patient-level characteristics should always be taken into consideration as with any complex medical condition.

Commonly utilized postinjury epochs include the immediate period (week 1), the acute period (weeks 1 to 6), the postacute or subacute period (weeks 7 to 12), and the chronic period thereafter. Many individuals recover briskly after concussion/mTBI within hours to days (typically 1 to 2 weeks), though symptoms may dissipate over several weeks in others. A frequently used benchmark for complete symptom resolution is 3 months, although some individuals remain symptomatic for weeks or even months afterward.

The majority of individuals with a history of concussion/mTBI can still expect a full recovery even if symptoms persist after 3 months. However, at least 10 to 25 percent of those with a history of concussion/mTBI may have a protracted symptom burden extending well beyond the traditionally quoted time periods noted above.[7] In this setting it may become challenging to disentangle unmasked or exacerbated premorbid conditions such as mood, headache, or sleep disorders from those persisting after injury. An additional complicating factor is that many of these same comorbid conditions may place an individual at risk for a protracted recovery course perhaps due to as-yet undefined pathophysiologic or psychosocial vulnerabilities. Moreover, neuroendocrine dysfunction is an under-recognized consequence of concussion/mTBI and, like impaired sleep, can accentuate symptom burden.

PATHOPHYSIOLOGY AND BIOMARKERS

Concussion/mTBI and more severe TBIs are linked by a common pathophysiology on a continuum of increasing complexity which is modified by (1) mechanism of injury; (2) the type, direction, and intensity of forces; and (3) a diversity of accompanying traumatic wounds including penetrating injuries, skull base fractures, intracranial lesions, and related conditions such as seizure or cerebral edema.[8] Subsequent secondary or tertiary systemic and neurologic abnormalities further propagate neurologic injury.

By historical definition, commonly used clinical neuroimaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) should not reveal brain structural abnormalities in concussion, and there should be no evidence of diffuse axonal injury, the so-called pathognomonic lesion of more severe injuries linked with potentially worse outcomes. Characterization of the underlying patterns and distribution of microstructural, biochemical, physiologic, and functional connectivity changes after concussion/mTBI is an active area of investigation using advanced noninvasive structural and functional neuroimaging techniques including diffusion tensor imaging, functional MRI, magnetoencephalography, and positron emission tomography.

Following concussion/mTBI, different central nervous system cell types release numerous substances, some of which are ultimately detectable in the systemic circulation. Many of these substances have been investigated for their utility as biomarkers, including glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal esterase L1 (UCH-L1), S100 calcium-binding protein B (S100-B), neuron-specific enolase (NSE), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) peptide, and tau. Tests measuring peripheral GFAP and UCH-L1 in particular have received FDA clearance to support acute diagnostic evaluations of adults with mTBI in the emergency setting, particularly to select individuals who should undergo brain imaging. However, a clinically indicated head CT even after such selection may not reveal acute abnormalities in patients presenting within concussion/mTBI. A proportion of these patients will demonstrate abnormalities on short-interval follow-up brain MRI that were undetectable on CT, excluding a diagnosis of concussion in favor of at least mild or complicated mild TBI. Recently, distinctly elevated plasma GFAP concentration measured within 24 hours of injury was shown to identify individuals likely to have abnormal MRI findings and, by proxy, ongoing follow-up needs, even when the initial head CT was negative.[9] GFAP levels were still elevated to a degree in MRI-negative mTBI cases compared with a control group. It is not yet known whether tracking plasma GFAP or other protein levels during recovery further stratifies clinical course. Combining measures from varying modalities may offer additional prognostic information. For care beyond the emergency department, most recent position statements and clinical practice guidelines do not yet recommend routine use of the above tests during recovery to guide management.

The heterogeneous clinical manifestations of concussion/mTBI reflect complex pathophysiologic mechanisms within and distal to the epicenters of brain injury, likely modulated by numerous patient-level features such as age at time of injury, type of injury, genetics, robustness and persistence of any innate inflammatory or other physiologic responses, and comorbid conditions. An ideal biomarker or set of biomarkers should be widely available, practical, inexpensive, and predictive of acute brain injury, recovery, and resolution. Recovery and return-to-activity guidance remain clinical determinations, necessitating systematic yet tailored treatment approaches until such markers are available. Symptom burden in the days following concussion/mTBI may be the currently most consistent predictor of slowed recovery.[10]

CLINICAL APPROACH

An organized diagnostic framework will allow accurate and swift determination that (1) a brain injury has occurred, even when the preceding event is atypical, particularly for those who do not present to the emergency department or urgent care clinic; (2) the symptoms experienced by an individual are actually a result of the injury; (3) there are no competing or complicating diagnoses (e.g., seizure, neurovascular lesions such as dissection, neurosurgical emergencies such as hematoma expansion); and (4) that investigation of reversible and treatable sequelae are undertaken. The latter often requires a thorough history and examination with judicious, targeted use of diagnostic tests such as neuroimaging, neuropsychologic testing, serum neuroendocrine screening, and specialty consultations. The manifestations of concussion/mTBI are highly variable and a patient may present to a number of different clinical venues or specialists before undergoing a comprehensive diagnosis. It is essential to emphasize to patients and to clinicians across multiple specialties that the consequences of concussion/mTBI are treatable.

Due to the tremendous variability in manifestations of concussion/mTBI, a patient may present to clinical care in late acute, subacute, or chronic phases with a debilitating milieu of symptoms. A systematic and domain-based evaluation creates a structured path forward for the patient, the primary or referring provider, and multidisciplinary care collaborators. The focus of care is multifaceted but includes safe, yet relatively prompt, return to usual activities. It is reasonable to select the most bothersome impairments, or the greatest barriers to usual activities, and target diagnostics and treatment strategies accordingly. Initial steps include allowing the patient to debrief regarding the injury while ascertaining date and mechanism of injury and severity classification. Important physical and neurobehavioral domains to query are noted in Table 37-1.

A detailed history paired with general and neurologic examinations will then allow for packaging of symptoms into distinct post-traumatic diagnoses, even if there is overlap of symptoms among domains. Diagnostic and treatment plans can then remain targeted and organized.

No single clinical examination maneuver, outcome measure, or set of outcome measures is uniformly applicable to all concussion/mTBI patients. However, position statements and clinical practice guidelines are updated regularly, highlight broadly used (and in some cases validated) instruments relevant to specific patient populations, and describe emerging techniques that can aid in diagnosis and treatment.[4–6] As

TABLE 37-1 ■ Manifestations of Concussion/Mild Traumatic Brain Injury

Post-traumatic Headache
Migraine phenomenology (e.g., photo-/phonophobia)
Tension-type headache
Occipital neuralgia
Other Pain
Pain in distribution of point of impact
Neck pain
"Dizziness"
Light-headedness
Vertigo
Imbalance
Orthostatic symptoms
Vision Changes
Vision loss (structural injury to optic nerve, retina)
Blurry vision (impaired accommodation)
Diplopia
Oscillopsia
Photophobia
Hearing Changes
Tinnitus
Phonophobia
Hearing loss
Neuroendocrine Dysfunction
Libido changes
Menstrual cycle irregularity
Erectile dysfunction
Mood impairment
Cognitive impairment
Cognitive Impairment
Short-term memory impairment
Inattention and other executive dysfunction
Slow processing
"Cognitive fog"
Mood Impairment
Exacerbated or de novo anxiety or depression
Irritability
Emotional dysregulation
PTSD
Affect changes
Fatigue
General fatigue
Excessive need for sleep
Exacerbated sleep disorders
Sleep Disturbance
Insomnia
Increased sleep duration
Frequent awakenings
Daytime somnolence
Symptoms suggestive of sleep apnea
Anosmia
Related weight changes
"History of Priors"
Timing and mechanisms of prior head injury
Headache history
Premorbid mood disorder(s)
Learning disability
Substance use
Family history of mood, cognitive, or learning disorders

Patients should be questioned about each individual domain. Common and/or often under-recognized sequelae are listed and suggested as prompts.

but one example, vestibular and vision system impairment is common after concussion/mTBI and the two systems have a high degree of overlap; the Vestibular/Ocular Motor Screening (VOMS) Assessment measures vestibular and oculomotor impairments by assessing eye movement smooth pursuits, saccades, near point convergence, vestibulo-ocular reflex (VOR), and visual motion sensitivity.[11] Impairments have been shown to identify individuals with sports-related concussion/mTBI. Taken in context with the clinical presentation and whole examination, the results from VOMS can inform subsequent consultation strategies (e.g., neuro-ophthalmology, neuro-otology, vestibular rehabilitation, vision therapy) while providing trackable metrics. In general, examination maneuvers and related diagnostic studies or consultations parallel the domains queried in Table 37-1.

When possible, measures documenting impairment or symptom severity should be tracked over time in order to gauge recovery trajectory or efficacy of treatment plans. Such measures should focus on observed or elicited clinical metrics and self-reported symptom

TABLE 37-2 ■ Suggested Approach to Diagnosis and Management

Post-traumatic Headache
Determine primary headache disorder semiology most consistent with presenting symptoms
Use established treatment strategies for the above disorder(s) including procedural interventions
Refer to consulting specialist if usual treatment strategies fail
Other Pain
Obtain physical therapy consultation (e.g., for cervical pain)
Consider comprehensive pain management/consultation
"Dizziness"
Determine etiology (e.g., central vs. peripheral vs. autonomic)
Arrange for formal balance evaluation
Refer to relevant consulting specialist
Arrange for vestibular rehabilitation
Vision Changes
Formal neuro-ophthalmologic evaluation
Formal balance testing
Consider vision therapy
Consider vestibular rehabilitation
Hearing Changes
Formal hearing test
Refer to relevant consulting specialist
Coping strategies (such as for tinnitus)
Consider migraine treatment, if appropriate, for phonophobia
Neuroendocrine Dysfunction
Serum neuroendocrine screen if indicated or if history of prior head injury, followed by referral to relevant specialist if abnormal
Cognitive Impairment
Address confounders (e.g., pain, mood, sleep)
Formal neuropsychologic evaluation and/or refer to specialist if persistent
Exclude reversible/treatable etiologies if persistent
Refer for neuroimaging if persistent
Refer for cognitive rehabilitation
Mood Impairment
Address confounders
Consider pharmacologic management
Refer to psychologist and/or psychiatrist (consider early referral in some cases)
Exclude reversible/treatable etiologies if persistent
Fatigue
Address confounders
Exclude reversible/treatable etiologies if persistent
Sleep Disturbance
Sleep hygiene counseling
Address confounders
Exclude reversible/treatable etiologies
Refer to relevant consulting specialist
Anosmia
Monitor weight
General Strategies
Abstinence from alcohol while symptomatic
Abstinence from activities that could lead to subsequent head injury during recovery
Consider testing only in chronic period, or 6–12 months after injury
Counseling regarding possible symptom triggers with cognitive, physical, or even emotional loads
Reassurance and education

Testing should be guided by the history and examination. Note overlapping confounders and strategies across many categories.

inventories. Unexplained focal neurologic signs or symptoms consistent with alternative diagnoses should prompt neuroimaging to exclude a structural cause. New signs or symptoms emerging after the first 1 to 2 weeks should also lower the threshold for neuroimaging or other indicated diagnostic studies. Targeted cognitive screening may be appropriate early after injury, depending on the patient population, to ensure impairments are within typical domains and not indicative of another condition. However, referral for full neuropsychologic evaluation for common complaints may not be warranted until confounders such as pain and sleep impairment are addressed. The VA/DoD Clinical Practice Guideline for Management of Concussion/mTBI recommends against comprehensive testing within the first 30 days of injury for service members with concussion/mTBI, particularly until competing diagnoses and confounders have been addressed.

Table 37-2 lists examples of potential diagnostic and therapeutic strategies for each domain listed in Table 37-1. For each category, ruling out red flags with urgent or emergent diagnostics is implied.

An additional "general strategies" category is also listed and is typically broadly applicable to most patients.

Many professional organizations recommend that clinicians educate patients via verbal and written material when possible regarding diagnosis, recovery, and clinic or emergency room return precautions. This material is typically available online through these organizations. In addition to these position statements, practice guidelines, and online patient-facing material, there are additional resources for the clinician which highlight practical management strategies for concussion/mTBI supported by evidence and longitudinal experience.[12]

Active Recovery

Active recovery approaches necessitate collaboration between the patient, family, and care team. The approach includes rapid identification and characterization of brain injury followed by targeted diagnostic and therapeutic programs that also involve patient education. In general, 1 to 2 days of rest is appropriate, including cognitive and physical rest with avoidance of overstimulation, followed by graded increases in usual activities with light to moderate intensity and with sufficient rest in between exposures provided the prescribed activities do not cause clinically significant symptoms. Symptom recrudescence may occur with increasing cognitive, physical, or even emotional challenges, and early expectation management and subsequent scaling of activity prescriptions may mitigate related distress, reluctance to engage in activity for fear of worsening injury, or any actual risk of injury exacerbation. It is important to note, however, protracted rest or abstinence from activities, if not clinically indicated, may lead to patient isolation and prolong symptom burden.

Prior dogma of strict physical activity limitations is also being challenged by emerging evidence supporting subthreshold aerobic exercise with escalating intensity, particularly in sports-related concussion/mTBI. One biologically plausible explanation in support of an exercise prescription relates to possible effects of aerobic exercise activity on cerebral blood flow. Autonomic nervous system function after concussion/mTBI may be impaired, especially if there are rotational forces transmitted through the brainstem during injury. These forces may cause microstructural changes affecting functionally connected processes such as altered peripheral and central sensitivity to the arterial partial pressure of carbon dioxide ($PaCO_2$), leading to inappropriate relative hypoventilation during exercise. Subsequent elevated $PaCO_2$ levels during aerobic activity increase cerebral blood flow (CBF) which may then exacerbate postconcussive symptoms, particularly early after injury. Training programs targeting subthreshold aerobic exercise may restore relevant sensitivity to $PaCO_2$, recalibrate CBF regulation, and ultimately reduce symptom exacerbation with increasing exercise intensity.[13] Aerobic exercise has thus been described as a treatment modality and a potential physiologic biomarker that parallels recovery (e.g., less postconcussive symptom recrudescence with ongoing training).[13] Most athletes presenting to clinic with concussion/mTBI should therefore be counseled to engage in graded light to moderate physical activity, after a brief period of initial rest, and should be referred to a physical therapist or other experienced professional for guidance with structured and studied programs such as the Buffalo Concussion Exercise Treatment Protocol.[3,13] Nonathlete patient populations may also benefit from this approach when supervised by an experienced therapist although this concept is not yet explicitly stated uniformly across position statements and practice guidelines. With careful counseling and safety screening, a patient may be able to conceptualize subthreshold aerobic exercise as a dose of medication even on days when prescribed physical activity has already occurred, or on days when the patient feels particularly unwell.[13]

The relationship between aerobic exercise and neuroplasticity is complex in patients with a history of acquired brain injuries of varying etiologies and severity. This is an active area of investigation targeted to identify periods of maximal benefit (and potential harm), establish frequency and intensity of exercise, and to more clearly characterize physiologic, neurobehavioral, and quality of life improvements. Exercise in general has clearly demonstrated powerful health advantages across disciplines for numerous medical conditions. Establishing a supervised exercise program with a goal toward an independent exercise routine and other usual activities may be a critical intervention with widespread benefits beyond concussion/mTBI treatment. Such a program provides additional structure to an active recovery approach and may empower the patient to self-administer treatments outside of prescribed therapy encounters. Counseling within the clinic, partnering with experienced therapists, and customizing plans for patients with a range of abilities or comorbid conditions will likely gain additional experimental support to enhance recovery. Screening for comorbid conditions is critical for harm reduction when prescribing exercise and should take into account an individual's medical history, medications, and functional abilities for prescription adaptation.

In addition to exercise as a treatment paradigm and the widely available educational material regarding graded activity exposure, customized return-to-activity plans should account for an individual's professional and personal obligations. As with exercise, a plan for a graded return to normal daily activity may be helpful.

Concussion Subtypes

Accumulating evidence supports distinct concussion/mTBI phenotypical subtypes characterized according to the primary symptomatic presentation. Subtypes include cognitive, ocular-motor, headache/migraine, vestibular, and anxiety/mood categories. Features of these subtypes are not mutually exclusive and may transition to other subtypes throughout recovery.[14] Current investigative strategies include using multimodal assessment techniques to fully characterize these proposed subtypes. Detailed clinical phenotypes may ultimately allow for earlier treatment target identification, more accurate prognostication, and refined treatment trial selection criteria. Position statements and guidelines do not yet discuss differences in management for these concussion subtypes, but in general targeting the most bothersome symptoms for diagnostic and treatment strategies is recommended.

SUBSEQUENT DEVELOPMENT OF NEURODEGENERATIVE DISEASE

Individuals who have sustained concussion/mTBI have common concerns related to prognosis, including the risk for developing neurodegenerative disease, particularly when cognitive impairment is a prominent presenting feature. More severe injuries have been linked with several neurodegenerative disorders including Alzheimer disease, Parkinson disease, and amyotrophic lateral sclerosis.[8,15] More recently, milder forms of head trauma including concussion/mTBI have been linked to increased risk for developing neurodegenerative disease. Patient-level factors that impact the link between TBI of any severity and neurodegenerative disease include genetics (e.g., APOE genotype status, α-synuclein genotype), age at which the injury was sustained, number and severity of repeated injuries, and various environmental exposures.[15] It is important to emphasize to the patient that many individuals with neurodegenerative conditions have not sustained head injuries, and many individuals with a history of head injury do not develop neurodegenerative disease. However, of equal importance is recognition of refractory cognitive and other neurobehavioral impairments beyond expected recovery curves following concussion/mTBI, particularly among certain presumably at-risk individuals (e.g., older adults, athletes, military personnel). These patients with refractory cognitive symptoms may warrant an expanded evaluation with relevant specialists in addition to usual concussion/mTBI clinical care.

A history of repetitive subconcussive or concussive head injuries has been identified as a risk factor for CTE. CTE is not a diagnosis that can occur during life but rather is a neuropathologic determination at autopsy. Determining the lifetime clinical correlates to CTE is an active area of investigation, and traumatic encephalopathy syndrome remains a research term used by investigators for related phenotyping studies. The neuropathology of CTE is unique among other neurodegenerative conditions and includes distribution of phosphorylated tau in perivascular neurons and astrocytes near cortical sulci, which are areas of particular vulnerability for axonal injury in head trauma. A large proportion of CTE cases also have other proteinopathies found in classic neurodegenerative diseases.[8] Precise impact quantity and severity thresholds and patient-level vulnerabilities that trigger the neuropathologic events leading to CTE are not yet known and are an area of active research. Regardless, there is an increasingly recognized framework that links repeat subconcussive and concussive injuries to clinical syndromes consistent with neurodegenerative disease, and ultimately a neuropathologic diagnosis of CTE. High-profile historical and recent literature has highlighted clinical syndromes among boxers thought to have CTE in retrospect, and confirmed CTE diagnoses have been made among other contact or collision sport athletes as well as military personnel.

Individuals with a history of multiple head injuries, head injuries in close succession, multiple subconcussive events, or sequentially more severe and more prolonged symptom burden following concussion/mTBI, should be engaged in discussions that weigh risks and benefits of ongoing exposure to the risk of subsequent injury. Currently, precise risk estimates of neurodegenerative disease are not available, but front-line clinicians are in a position to identify lingering or progressive neurobehavioral signs and symptoms despite appropriate and maximal medical management and then redirect diagnostic and treatment strategies accordingly. This approach should be considered in the appropriate clinical context even after a single concussion/mTBI, given compelling epidemiologic study results.[15]

CONCLUDING COMMENTS

Concussion/mTBI is a treatable entity despite highly variable clinical manifestations and is best addressed early after injury and with a systematic approach. Patient-level features may impact recovery trajectories. Persistent postconcussive symptoms may be approached in the same way as symptoms that occur in the acute or subacute period. Prolonged persistent postconcussive symptoms may also be complicated by, or even a result of, concurrent medical conditions, and caution should be used when attributing symptom profiles to a remote head injury. Currently, number and severity of immediate postinjury symptoms is the strongest predictor of prolonged recovery. Assessments should include clinical, cognitive, behavioral, and symptom burden measures to capture the entirety of treatable postconcussive sequelae and to gauge recovery in order to develop tailored return-to-activity guidance. Lingering or progressive cognitive or neurobehavioral symptoms may warrant expanded evaluation. Given the current lack of acute or prophylactic neuroprotective treatments for the moment of impact, select individuals at risk for ongoing exposure to subconcussive or concussive traumatic injury should be identified and engaged in a return-to-activity dialogue. Active recovery includes a multifaceted approach to gradual increase in usual activities until symptom resolution and avoids prolonged rest. Treatment paradigms are shifting toward increasingly evidence-based methods that will likely remain multifaceted. Biomarkers are needed to identify injury, track recovery and resolution, and flag risk for repeat or progressive injury despite optimal medical management, and a number of promising techniques are undergoing active investigation.

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SECTION

11

Infections, Inflammatory, and Immunologic Disorders

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CHAPTER

38

Acute Bacterial Infections of the Central Nervous System

KYLE J. COLEMAN ■ KAREN L. ROOS

ACUTE BACTERIAL MENINGITIS
- Etiology
- Clinical Presentation
- Diagnosis
- Differential Diagnosis
  - *Viral Meningitis*
  - *Herpes Simplex Virus Encephalitis*
  - *Arthropod-Borne Virus Encephalitis*
  - *Rocky Mountain Spotted Fever*
  - *Focal Infectious Intracranial Mass Lesions*
  - *Subarachnoid Hemorrhage*
- Treatment
  - *Empiric Antimicrobial Therapy*
  - *Specific Antimicrobial Therapy*
  - *Dexamethasone Therapy*
- Prevention

BRAIN ABSCESS
- Etiology
- Clinical Presentation
- Diagnosis
- Differential Diagnosis
- Treatment

SUBDURAL EMPYEMA AND CRANIAL EPIDURAL ABSCESS
- Etiology
- Clinical Presentation
- Diagnosis
- Treatment

SPINAL EPIDURAL ABSCESS
- Etiology
- Clinical Presentation
- Diagnosis
- Treatment

SEPTIC INTRACRANIAL THROMBOPHLEBITIS
- Etiology
- Clinical Presentation
- Diagnosis
- Treatment

Acute bacterial infections of the central nervous system (CNS) include meningitis, brain abscess, subdural empyema, epidural abscess, and septic intracranial thrombophlebitis. The etiology, clinical presentation, diagnosis, and treatment of each of these bacterial infections are discussed in this chapter.

ACUTE BACTERIAL MENINGITIS

Bacterial meningitis is an acute purulent infection in the subarachnoid space, associated with an inflammatory reaction in the brain parenchyma and cerebral vasculature. During its treatment, not only must the meningeal pathogen be eradicated, but also the neurologic complications resulting from an often robust inflammatory reaction must be anticipated and managed. The most common causative organisms of bacterial meningitis are *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria monocytogenes*, *Staphylococcus aureus*, group B streptococci, and gram-negative bacilli. The current epidemiology of acute bacterial meningitis, the best diagnostic tests to perform on cerebrospinal fluid (CSF), the use of dexamethasone as adjunctive therapy, and the present recommendations for the use of chemoprophylaxis and vaccination are discussed here.

Etiology

The most common etiologic organisms of acute bacterial meningitis in children and adults are *S. pneumoniae* and *N. meningitidis*. Prior to the routine use of the *Haemophilus influenzae* type b conjugate vaccine,

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H. influenzae type b was the most common cause of bacterial meningitis in children in the United States. Use of this vaccine has dramatically reduced the incidence of bacterial meningitis due to *H. influenzae* type b in children. *H. influenzae* type b, however, remains an important cause of bacterial meningitis in older adults, immunocompromised patients, and patients with chronic lung disease, splenectomy, leukemia, or sickle cell anemia. Children too young to have completed a primary *H. influenzae* type b vaccination course are also at risk.

S. pneumoniae is the most common cause of community-acquired meningitis in both children and adults in the United States and Europe. A number of predisposing conditions increase the risk of pneumococcal meningitis, the most common of which is pneumonia. Acute and chronic otitis media, sinusitis, immunodeficiency from alcoholism, diabetes, cancer, and immunosuppressive drugs are also important risk factors. Given the rise of multidrug-resistant strains of *S. pneumoniae* to both penicillin and third-generation cephalosporins, vancomycin is added to the initial empiric antimicrobial therapy, with specific antibiotic therapy based on culture susceptibilities.[1]

N. meningitidis is the second most common cause of meningitis in adults, but has a predilection for those younger than age 60. The quadrivalent (serogroups A, C, W-135, and Y) meningococcal glycoconjugate vaccine is recommended for all 11- to 18-year-olds, and is a requirement for attending most colleges and universities in the United States. A vaccine for serogroup B became available in 2015 and is increasingly recommended for college-bound students.

The Enterobacteriaceae (*Proteus* species, *Escherichia coli*, *Klebsiella* species, *Serratia* species, and *Enterobacter* species) cause meningitis in older adults; in adults with underlying diseases such as cancer, diabetes, alcoholism, congestive heart failure, chronic lung disease, and hepatic or renal dysfunction; and in neurosurgical patients.

L. monocytogenes is a cause of meningitis in individuals with impaired cell-mediated immunity from older age (adults greater than 55 years old), organ transplantation, pregnancy, malignancy, chronic illness, immunosuppressive therapy, and neonates. Outbreaks have occurred from eating contaminated foods. The incidence amongst pregnant women and neonates has decreased, likely from education on foodborne infections during pregnancy.[2] In addition, the routine use of trimethoprim-sulfamethoxazole as a prophylactic agent for the prevention of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome (AIDS) has the added benefit of reducing the risk of *L. monocytogenes* infection, including meningitis.

S. aureus and coagulase-negative staphylococci are the predominant organisms causing meningitis as a complication of invasive neurosurgical procedures, particularly shunting procedures for hydrocephalus and with subcutaneous Ommaya reservoirs or following lumbar puncture for the administration of intrathecal chemotherapy. Hematogenous spread accounts for 25 percent of *S. aureus* meningitis cases and is seen in patients with endocarditis, pneumonia, and skin or soft-tissue infections. Intravenous drug use accounts for an increasing number of methicillin-resistant (MRSA) infections.

Streptococcus agalactiae, or group B streptococcus, is a leading cause of bacterial meningitis and sepsis in neonates and is increasingly recognized in two groups of adults: puerperal women and patients with serious underlying disease.

Clinical Presentation

The classic triad of symptoms and signs of bacterial meningitis consists of fever, headache, and stiff neck. An altered level of consciousness, such as lethargy or stupor, may deteriorate rapidly, and should be added to the classic triad for potential bacterial meningitis. Approximately 95 percent of patients will have at least two of the four symptoms and signs of fever, stiff neck, headache, or altered mental status, but less than 50 percent will have all three components of the classic triad.[3] Nausea, vomiting, and photophobia are common complaints, which often reflect elevated intracranial pressure (ICP). Seizure activity occurs in approximately 20 percent of patients, although in neonates this can approach 40 percent, typically either at the onset or within the first few days of the illness; seizures are a poor prognostic indicator.[1]

A stiff neck, or meningismus, is the pathognomonic sign of meningeal irritation. Meningismus is present when the neck resists passive flexion. Kernig and Brudzinski signs are classic signs of meningeal irritation with high specificities but relatively low sensitivities, and therefore their absence does not exclude the diagnosis. Kernig sign is elicited with the patient in the supine position; the thigh is flexed on the abdomen, with the knee flexed. Attempts to passively extend the leg elicit pain when meningeal irritation is present. Brudzinski sign is elicited with the patient in a supine position and is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees.

Increased ICP is an expected complication of bacterial meningitis and is the major cause of obtundation and coma. The most common signs of increased ICP in bacterial meningitis are an altered level of consciousness and papilledema. Cerebral arteritis and septic venous thrombosis of the cerebral dural sinuses and cortical veins are also complications of bacterial meningitis, often presenting as focal neurologic deficits or as new-onset seizure activity.

The rash of meningococcemia begins as a diffuse erythematous maculopapular rash resembling a viral exanthem, but the lesions rapidly become petechial. This rash can be differentiated from the rash of a viremia in that petechiae are found on the trunk and lower extremities in meningococcemia. Petechiae may also be found in the mucous membranes and conjunctiva and occasionally on the palms and soles. Other infectious diseases that may manifest with a petechial, purpuric, or erythematous maculopapular rash resembling that of meningococcemia include enteroviral meningitis, Rocky Mountain spotted fever, West Nile virus encephalitis, bacterial endocarditis, echovirus type 9 viremia, and, more rarely, pneumococcal or *H. influenzae* meningitis.

Diagnosis

The diagnosis of bacterial meningitis is made by examination of the CSF. The necessity of neuroimaging prior to lumbar puncture has been debated for years. The presence of any of the following necessitate neuroimaging prior to lumbar puncture: an altered level of consciousness, papilledema, focal neurologic deficits, an immunocompromised state, or new-onset seizure activity. When the clinical presentation is suggestive of bacterial meningitis, two sets of blood cultures should be obtained and dexamethasone and empiric antimicrobial therapy initiated immediately. If the patient is being treated with antibiotics, there is no risk in delaying lumbar puncture until after neuroimaging has been performed. While antibiotics do decrease the likelihood of a positive CSF culture, the culture is still positive in approximately 75 percent of cases if obtained less than 4 hours after antibiotic initiation, since it takes time to sterilize the cultures once antibiotics have been initiated. Antibiotic therapy for several hours prior to lumbar puncture has little effect on CSF white blood cell count or glucose concentration, so even if the specific organism is not isolated, the overall suspicion of bacterial meningitis based on CSF abnormalities will remain. Blood cultures are positive at least 60 percent of the time, making them particularly helpful if CSF culture is negative. Serum procalcitonin is elevated in bacterial, but not viral, meningitis.

The classic CSF abnormalities in bacterial meningitis are: (1) an increased opening pressure (>18 cm water); (2) a pleocytosis of polymorphonuclear leukocytes (10 to 10,000 WBCs/mm^3); (3) a decreased glucose concentration (<40 mg/dL or CSF/serum glucose ratio of <0.31); and (4) an increased protein concentration. A CSF sample should be analyzed using Gram stain and bacterial culture, which can identify the causative pathogen in approximately 80 percent of patients. CSF PCR assays detect bacterial nucleic acid in CSF. A 16S rRNA conserved sequence broad-based bacterial PCR can detect small numbers of viable and nonviable organisms in the CSF, but this assay has been replaced by newer nucleic acid assays.

A commonly used PCR panel is the FilmArray Meningitis/Encephalitis panel which tests six bacterial meningeal pathogens, including *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, *E. coli*, group B streptococcus and *L. monocytogenes*. Specific advantages of this PCR panel are its rapid turnaround time, which can be as short as 1 hour, and that antibiotics do not interfere with its results. The sensitivity and specificity of the FilmArray Meningitis/Encephalitis panel for bacterial pathogens is not known at this time as further studies are still required for verification along with further refinements to reduce false-positive rates. Metagenomic next-generation sequencing (mNGS) is a newer nucleic acid assay to identify the meningeal pathogen.[4] A limitation to mNGS is that the results take time. Metagenomic next-generation sequencing is particularly helpful in those instances when the pathogen is difficult to detect. PCR assays have eliminated the need for previously used tests, such as the latex particle agglutination test, which had high specificities but variable sensitivities. A false-positive PCR is a possibility with meningitis/encephalitis panels and mNGS. The results of a PCR assay can be confirmed by a conventional test, such as culture, CSF IgM, acute and convalescent serology, or some combination of these tests. In clinical practice, when bacterial meningitis is a possibility, most physicians treat with empiric therapy until CSF analysis suggests an alternative diagnosis.

If there are petechial skin lesions, biopsies should be performed. While the occurrence of a rash is only modestly sensitive, it is highly specific for meningococcal meningitis if present. The rash of meningococcemia results from the dermal seeding of organisms with vascular endothelial damage, and biopsy may reveal the organism on Gram stain.

Lumbar puncture should be performed with a 22- or 25-gauge needle. The amount of CSF recommended for testing is 10 to 15 ml, which includes saving 5 ml for future testing. Cell count with differential, glucose and protein concentrations, Gram stain and culture, and viral culture and PCR assays all should be sent and more advanced testing including panels and mNGS should be considered as above in some clinical situations.

Differential Diagnosis

Viral meningitis and herpes simplex virus (HSV) encephalitis are the leading diseases in the differential diagnosis of bacterial meningitis. Arthropod-borne viral encephalitis should be considered during the summer and early fall months while mosquitoes are biting. Focal intracranial mass lesions and subarachnoid hemorrhage also need to be included in the differential diagnosis when approaching patients with suspected meningitis.

VIRAL MENINGITIS

In a patient with fever, headache, and a stiff neck, the leading consideration in addition to bacterial meningitis, is viral meningitis. The key difference is that patients with viral meningitis do not typically have an altered level of consciousness and are both awake and alert. Patients with viral meningitis will often be sitting up and concerned about the severity of their headache. Patients with viral meningitis also do not have seizures or focal neurologic deficits. In addition to clinical differences, viral meningitis will have a distinct CSF profile from bacterial meningitis. In comparison to the predominantly polymorphonuclear pleocytosis and low glucose concentration of bacterial meningitis, patients with viral meningitis will exhibit a lymphocytic pleocytosis with a modest white cell count (often 100 to 500 WBCs) and normal glucose concentration. Treatment for viral meningitis is largely supportive, except when the organism is herpes simplex virus (HSV) or varicella zoster virus (VZV), in which case acyclovir, valacyclovir, or famciclovir should be used. Viral meningitis is typically a self-limited disease, but the headache may take months to resolve.

HERPES SIMPLEX VIRUS ENCEPHALITIS

The clinical presentation of HSV encephalitis (discussed in detail in Chapter 42) often includes hemicranial headache, fever, behavioral abnormalities, focal or generalized seizure activity, and focal neurologic deficits (e.g., dysphasia, usually hemiparesis with greater involvement of the face and arm, and superior visual field defects). The symptoms of HSV encephalitis typically evolve over several days, and the presentation is often less acute than bacterial meningitis. In patients with HSV encephalitis, fluid-attenuated inversion recovery (FLAIR), T2-, and diffusion-weighted magnetic resonance imaging (MRI) sequences demonstrate lesions in the medial and inferior temporal lobe, inferior frontal lobe, and insular cortex that begin unilaterally and remain asymmetric if contralateral involvement occurs. Lesions will have associated edema, restricted diffusion (particularly early in the course), hemorrhage, or some combination of these features. The absence of an abnormality on MRI 48 hours after symptom onset should prompt consideration of another diagnosis.

There is a distinctive electroencephalographic (EEG) pattern in HSV encephalitis, consisting of periodic, stereotyped complexes from one or both temporal areas that occur at regular intervals of 1 to 2 seconds and are typically observed between day 2 and day 15 of the illness. Examination of the CSF reveals an increased opening pressure, a lymphocytic pleocytosis of 5 to 500 cells/mm^3, a mild to moderate elevation in the protein concentration, and a normal or mildly decreased glucose concentration. There may be red blood cells or xanthochromia, findings that reflect the hemorrhagic nature of the encephalitis but are neither sensitive nor specific markers of the disorder. Results of CSF viral cultures for HSV-1 are almost always negative.

HSV PCR is the gold standard for diagnosis with a sensitivity of 96 percent and specificity of 99 percent. Nonetheless, a false-negative PCR is possible within the first 72 hours of symptom onset. If an initial CSF HSV PCR is negative within the first 72 hours of symptoms and HSV remains a major diagnostic consideration, patients should be continued on empiric treatment and repeat lumbar puncture with HSV PCR should be performed 3 to 7 days later. CSF and serum samples can also be sent for HSV IgG antibody titers if neurologic symptoms are present for more than 1 week at the time of presentation, since the sensitivity of HSV PCR begins to decline after the first week and antibodies to HSV appear in the CSF approximately 8 to 12 days after onset of symptoms. A serum to CSF HSV-1 antibody ratio of less than 20 to 1 is considered diagnostic of intrathecal synthesis of antibodies and HSV encephalitis in the appropriate clinical context.

ARTHROPOD-BORNE VIRUS ENCEPHALITIS

During the summer and early fall months when mosquitoes are active, arthropod-borne virus (also known as arbovirus) encephalitis (see Chapter 42) should be included in the differential diagnosis of patients with meningitis. In the United States, the most common arbovirus is West Nile virus with the number of neuroinvasive cases ranging from a few hundred to a few thousand cases per year. The other arboviruses occur much less frequently, and include St. Louis encephalitis virus, Powassan virus, La Crosse virus, western equine encephalitis virus, Jamestown Canyon virus, and eastern equine encephalitis virus.[5] Eastern equine encephalitis virus causes the most severe arthropod-borne viral encephalitis, and the fatality rate is as high as 40 percent; recent outbreaks of this rare disease have raised awareness of the entity. Japanese encephalitis virus is the most common cause of arboviral encephalitis worldwide and occurs mainly in Asia. Venezuelan equine encephalitis virus is endemic in South America and is a rare cause of encephalitis in Central America and the southwestern United States, particularly in Texas.

The clinical presentation of arthropod-borne viral encephalitis, regardless of the specific virus, is fairly characteristic. The onset of encephalitic symptoms may be preceded by an influenza-like prodrome of fever, malaise, myalgias, nausea, and vomiting followed by headache, confusion, stupor, and occasionally convulsions. Focal neurologic deficits and focal seizure activity have been reported in cases of encephalitis caused by eastern equine encephalitis virus and La Crosse virus. Patients with West Nile virus encephalitis may have conjunctivitis or a maculopapular or roseolar rash. Patients with West Nile virus or St. Louis encephalitis virus may present with a polio-like acute asymmetric flaccid weakness or a syndrome of tremors, myoclonus, or parkinsonian features. The flaviviruses, including St. Louis encephalitis virus, Japanese encephalitis virus, and West Nile virus, tend to infect the basal ganglia and the thalamus, leading to tremors during the acute disease and a parkinsonian-like syndrome in survivors.

On neuroimaging, bilateral and symmetric T2-FLAIR hyperintensities with associated mass effect in the basal ganglia and thalamus are a characteristic finding in eastern equine encephalitis virus, St. Louis encephalitis virus, Japanese encephalitis virus, and West Nile virus encephalitis.

Examination of the CSF demonstrates a polymorphonuclear leukocytic pleocytosis if tested very early in the course, and this typically evolves to a moderate lymphocytic pleocytosis (i.e., several hundred cells). The CSF glucose concentration and protein concentration are usually normal. Based on criteria established by the US Centers for Disease Control and Prevention, a confirmed case of arboviral encephalitis is defined as a febrile illness with encephalitis during a period when arboviral transmission is likely to occur, plus at least one of the following: (1) fourfold or greater rise in serum antibody titer between the time of acute illness and 4 weeks later; (2) isolation of virus from tissue, blood, or CSF; or (3) a specific immunoglobulin M (IgM) antibody identified in the CSF. However, La Crosse virus has not been isolated from CSF and St. Louis encephalitis virus, eastern equine encephalitis virus, and western equine encephalitis virus are rarely isolated from CSF; therefore antibody titers are typically the diagnostic test of choice. A CSF PCR assay is available for the detection of West Nile virus nucleic acid and has a high specificity; however, it has a low sensitivity so a negative test does not exclude the disorder. The detection of West Nile virus IgM in CSF is considered the most sensitive diagnostic test for West Nile virus encephalitis. West Nile virus IgM antibodies may persist in serum (not the CSF) for a year or more after exposure to the virus and therefore cannot be used for definitive diagnosis of recent infection.

ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever is caused by the bacterium *Rickettsia rickettsii*. The disease begins with high fever, prostration, myalgias, headache, nausea, and vomiting. The rash is characteristic and presents initially as a diffuse erythematous maculopapular eruption appearing 2 to 4 days after the onset of symptoms, usually beginning at the wrist and ankles and then spreading distally, including to the palms and soles, and then proximally within a matter of a few hours. Diagnosis is made by immunofluorescent staining of skin biopsy specimens or by the detection of IgM and IgG antibodies. If a tick-borne etiology is suspected, then empiric treatment with doxycycline should be initiated.

Focal Infectious Intracranial Mass Lesions

Focal infectious intracranial mass lesions, including brain abscess, subdural empyema, and epidural abscess, are discussed later in this chapter but should be included in the differential diagnosis of bacterial meningitis. The presence of a focal infectious intracranial mass lesion is suggested by focal or generalized seizure activity or focal neurologic deficits on examination. This possibility is ruled out by neuroimaging.

Subarachnoid Hemorrhage

The possibility of a subarachnoid hemorrhage should also be included in the differential diagnosis of acute bacterial meningitis. The clinical presentation is characterized by the explosive onset of a severe headache or a sudden transient loss of consciousness followed by a severe headache. Because of the presence of blood in the subarachnoid space, nuchal rigidity is frequently present, leading to diagnostic confusion with infectious meningitis. A dilated nonreactive pupil is suggestive of a subarachnoid hemorrhage from an aneurysm of the posterior communicating artery. Computed tomography (CT) of the brain may demonstrate blood in the basal cisterns. If the CT scan is normal, the spinal fluid should be examined for red blood cells and xanthochromia. Red blood cells are present in the CSF within minutes of the rupture of an intracranial aneurysm and usually fail to clear in successive tubes of CSF. A sample of the blood-tinged CSF should be centrifuged; a yellow or xanthochromic color in the supernatant is present 6 to 12 hours following subarachnoid hemorrhage and lasts for 2 to 3 weeks. Xanthochromic spinal fluid may also be seen when the CSF protein concentration is elevated (above 150 to 200 mg/dL), and therefore it can be seen in bacterial meningitis.

Treatment

Empiric Antimicrobial Therapy

TABLE 38-1 ■ Empiric Therapy for Acute Bacterial Meningitis in Children and Adults

Community-acquired (immunocompetent child or adult)	Cefotaxime or ceftriaxone or cefepime *plus* Vancomycin *plus* Acyclovir
Community-acquired (immunosuppressed individual)	Cefotaxime or ceftriaxone or cefepime *plus* Vancomycin *plus* Acyclovir *plus* Ampicillin
Iatrogenic (associated with neurosurgery, epidural anesthesia, intrathecal chemotherapy)	Vancomycin *plus* Ceftazidime or meropenem

When bacterial meningitis is suspected, antimicrobial therapy is initiated immediately after blood cultures are obtained and before the results of CSF Gram stain, culture, and antimicrobial susceptibility tests are known. Empiric therapy should be based on the possibility that the patient has penicillin- and cephalosporin-resistant pneumococcal meningitis and should include a combination of a third- (ceftriaxone or cefotaxime) or fourth-generation cephalosporin (cefepime) plus vancomycin. Acyclovir is added to the empiric regimen to cover HSV (Table 38-1). Ampicillin should be added to cover *L. monocytogenes* if the patient is over the age of 55 years or is immunosuppressed. When the patient has been treated with trimethoprim-sulfamethoxazole for prophylaxis of toxoplasmosis or *P. carinii* pneumonia, it is less likely that the meningitis is due to *L. monocytogenes*. Meningitis that complicates a neurosurgical procedure, epidural anesthesia, head trauma with skull base fracture, or intrathecal chemotherapy should be treated empirically with a combination of vancomycin plus ceftazidime, cefepime, or meropenem. Vancomycin is used to cover staphylococci and ceftazidime, cefepime, or meropenem to cover gram-negative bacilli, specifically *Pseudomonas aeruginosa*. The doses of each of the antimicrobial agents are provided in Table 38-2, which shows both pediatric and adult dosing ranges.

Specific Antimicrobial Therapy

All CSF bacterial isolates should be tested for antimicrobial susceptibility. In experimental models of bacterial meningitis, the maximal bactericidal activity occurs when the antibiotic concentration is 10 to 30 times greater than the minimal bactericidal concentration of the microorganism in vitro.[6]

Pneumococcal Meningitis

Antimicrobial therapy for pneumococcal meningitis is initiated with a third- or fourth-generation cephalosporin

TABLE 38-2 ■ Doses of Antimicrobial Agents

Antimicrobial Agent	Total Daily Pediatric Dose (Dosing Interval)	Total Daily Adult Dose (Dosing Interval)
Acyclovir	30 mg/kg daily (every 8 h)	30 mg/kg daily (every 8 h)
Ampicillin	300 mg/kg daily (every 6 h)	12 g/day (every 4–6 h)
Cefepime	150 mg/kg daily (every 8 h)	6 g/day (every 8 h)
Cefotaxime	225–300 mg/kg daily (every 6–8 h)	12 g/day (every 4–6 h)
Ceftazidime	150–200 mg/kg daily (every 8 h)	8 g/day (every 8 h)
Ceftriaxone	80–100 mg/kg daily (every 12 h)	4 g/day (every 12 h)
Meropenem	120 mg/kg daily (every 8 h)	6 g/day (every 8 h)
Metronidazole	30 mg/kg daily (every 6 h)	2 g/day (every 6 h)
Nafcillin	200 mg/kg daily (every 6 h)	12 g/day (every 4 h)
Penicillin G	0.3 million U/kg/day (every 4–6 h)	24 million U/day (every 4–6 h)
Vancomycin	60 mg/kg daily (every 6 h)	45–60 mg/kg daily (every 6 h)
Intrathecal vancomycin	10 mg/day	20 mg/day

TABLE 38-3 ■ Specific Antimicrobial Therapy for Bacterial Infections of the Central Nervous System

Organism	Antibiotic
Streptococcus pneumoniae	
Sensitive to penicillin	Penicillin G *or* ceftriaxone *or* cefotaxime
Relatively resistant to penicillin	Ceftriaxone *or* cefotaxime
Resistant to penicillin	Vancomycin *plus*
	Cefotaxime *or* ceftriaxone +/− intraventricular vancomycin
Neisseria meningitidis	Ceftriaxone *or* penicillin G *or* ampicillin
Staphylococci	
Methicillin-sensitive	Nafcillin
Methicillin-resistant	Vancomycin
Listeria monocytogenes	Ampicillin
Enterobacteriaceae	Cefotaxime *or* ceftriaxone *or* cefepime
Pseudomonas aeruginosa	Ceftazidime *or* cefepime *or* meropenem
Haemophilus influenzae	Ceftriaxone
Streptococcus agalactiae	Ampicillin *or* penicillin G
Anaerobes	Metronidazole
Nocardia asteroides	Trimethoprim-sulfamethoxazole
Bacteroides species	Metronidazole

and vancomycin. Rifampin can be added to vancomycin for its synergistic effect because it is highly active against most penicillin-resistant pneumococci, but rifampin is inadequate as monotherapy because resistance develops rapidly. Some strains of pneumococci are sensitive to penicillin. Once the results of antimicrobial susceptibility tests are known, therapy can be modified accordingly (Table 38-3).

For pneumococcal meningitis, consideration should be given to using intraventricular vancomycin in patients not responding to parenteral vancomycin. The intraventricular route of administration is preferred over the intrathecal route because adequate concentrations of vancomycin in the cerebral ventricles are not always achieved with intrathecal administration. Intraventricular and intrathecal vancomycin is safe and is not associated with a risk of seizure activity. A 2-week course of intravenous antimicrobial therapy is recommended for pneumococcal meningitis.

Meningococcal Meningitis

Penicillin G or a third-generation cephalosporin (Table 38-3) remains the antibiotic of choice for meningococcal meningitis. Isolates of *N. meningitidis* with moderate or relative resistance to penicillin [defined as a minimal inhibitory concentration (MIC) of penicillin of 0.12 to 0.25 μg/mL] and decreased susceptibility to ampicillin have been reported from a wide variety of geographic locations. All CSF isolates of *N. meningitidis* should be tested for penicillin and ampicillin susceptibility. If antimicrobial susceptibility testing demonstrates that the isolate is a relatively penicillin-resistant strain, or if the patient is in an area with a high prevalence of meningococci with decreased susceptibility to penicillin, cefotaxime or ceftriaxone should be used. A 7-day course of intravenous antibiotic therapy is adequate for most uncomplicated cases of meningococcal meningitis. The index case and all close contacts should receive chemoprophylaxis with a 2-day regimen of rifampin (600 mg every 12 hours for 2 days in adults and 10 mg/kg every 12 hours for 2 days in children older than 2 years of age). Rifampin should not be used in pregnant women. Pregnant and lactating women and children less than 2 years of age may be given intravenous or intramuscular ceftriaxone, in a single injection of 250 mg for adults and 125 mg for children. Close contacts are defined as individuals who have had contact with nasopharyngeal secretions either through kissing or sharing toys, beverages, or cigarettes.

Staphylococcal Meningitis

Meningitis caused by *S. aureus* or coagulase-negative staphylococci is treated with nafcillin or oxacillin. Vancomycin is the drug of choice for methicillin-resistant staphylococci and for patients allergic to penicillin. Linezolid is the drug of choice for vancomycin-resistant strains (MIC $>$ 2.0 μg/mL). Treatment is for a minimum of 14 days. The CSF should be monitored during therapy, and if the spinal fluid continues to yield viable organisms after 48 hours of intravenous therapy, intraventricular vancomycin, 10 mg once daily for children or 20 mg once daily for adults, should be added.

Listeria monocytogenes Meningitis

Meningitis due to *L. monocytogenes* is treated with ampicillin for at least 3 weeks. Gentamicin should be added to ampicillin in critically ill patients. Meningitis caused by this organism is seen less often today in immunosuppressed patients than in the past because of trimethoprim-sulfamethoxazole administration in these patients as prophylaxis against *P. carinii* pneumonia and toxoplasmosis.

Enterobacteriaceae Meningitis

Meningitis caused by the Enterobacteriaceae, including *Proteus* species, *E. coli*, *Klebsiella* species, *Serratia* species, and *Enterobacter* species, is treated with a third- or fourth-generation cephalosporin, either cefotaxime, ceftriaxone, or cefepime, for 3 weeks.

Pseudomonas aeruginosa Meningitis

The third-generation cephalosporins, cefotaxime, ceftriaxone, and ceftazidime are equally efficacious for the treatment of gram-negative bacillary meningitis, with the exception of meningitis caused by *P. aeruginosa*. Meningitis resulting from infection with this organism is treated with ceftazidime, cefepime, or meropenem intravenously for 3 weeks.

DEXAMETHASONE THERAPY

The use of dexamethasone as adjunctive therapy in bacterial meningitis comes from the present understanding of the pathophysiology of the neurologic complications of bacterial meningitis. The critical event in pathogenesis is the inflammatory reaction in the subarachnoid space to the invading meningeal pathogen. The pathogen itself is not responsible for most neurologic complications. In bacterial meningitis, damage to the CNS progresses long after the CSF has been sterilized by antibiotic therapy.

Lysis of bacteria and release of bacterial cell wall components into the subarachnoid space are the initial steps in the induction of the inflammatory process and formation of a purulent exudate (Fig. 38-1). Components of bacterial cell walls, such as lipopolysaccharide molecules (endotoxin), a cell wall component of gram-negative bacteria, and teichoic acid and peptidoglycan, cell wall components of the pneumococcal species, induce meningeal inflammation by stimulating the production of inflammatory cytokines and chemokines by microglia (CNS macrophage-equivalent cells), astrocytes, monocytes, microvascular endothelial cells, and white blood cells in the CSF space. There are a number of consequences that result from the presence of inflammatory cytokines in CSF. Tumor necrosis factor (TNF) and interleukin-1 (IL-1) act synergistically to alter the permeability of the blood—brain barrier, allowing for the leakage of serum proteins and other molecules into the CSF and contributing to the formation of a purulent exudate. This purulent exudate may obstruct the flow of CSF through the ventricular system and diminish the resorptive capacity of the arachnoid granulations in the dural sinuses, leading to nonobstructive or communicating hydrocephalus and to interstitial edema. The exudate also surrounds and narrows the diameter of the lumen of the large arteries at the base of the brain with infiltration of inflammatory cells in the arterial walls (i.e., vasculitis). These inflammatory cytokines also recruit polymorphonuclear leukocytes from the blood stream and upregulate the expression of selectins on cerebral capillary endothelial cells and leukocytes, which allow for migration of leukocytes into the CSF.

Experimental models of meningitis suggest that bacterial eradication is not a leukocyte-dependent phenomenon. Neutrophils degranulate and release toxic metabolites that contribute to cytotoxic edema, cell injury, and death. The adherence of leukocytes to cerebral capillary endothelial cells increases the permeability of blood vessels, allowing for the leakage of

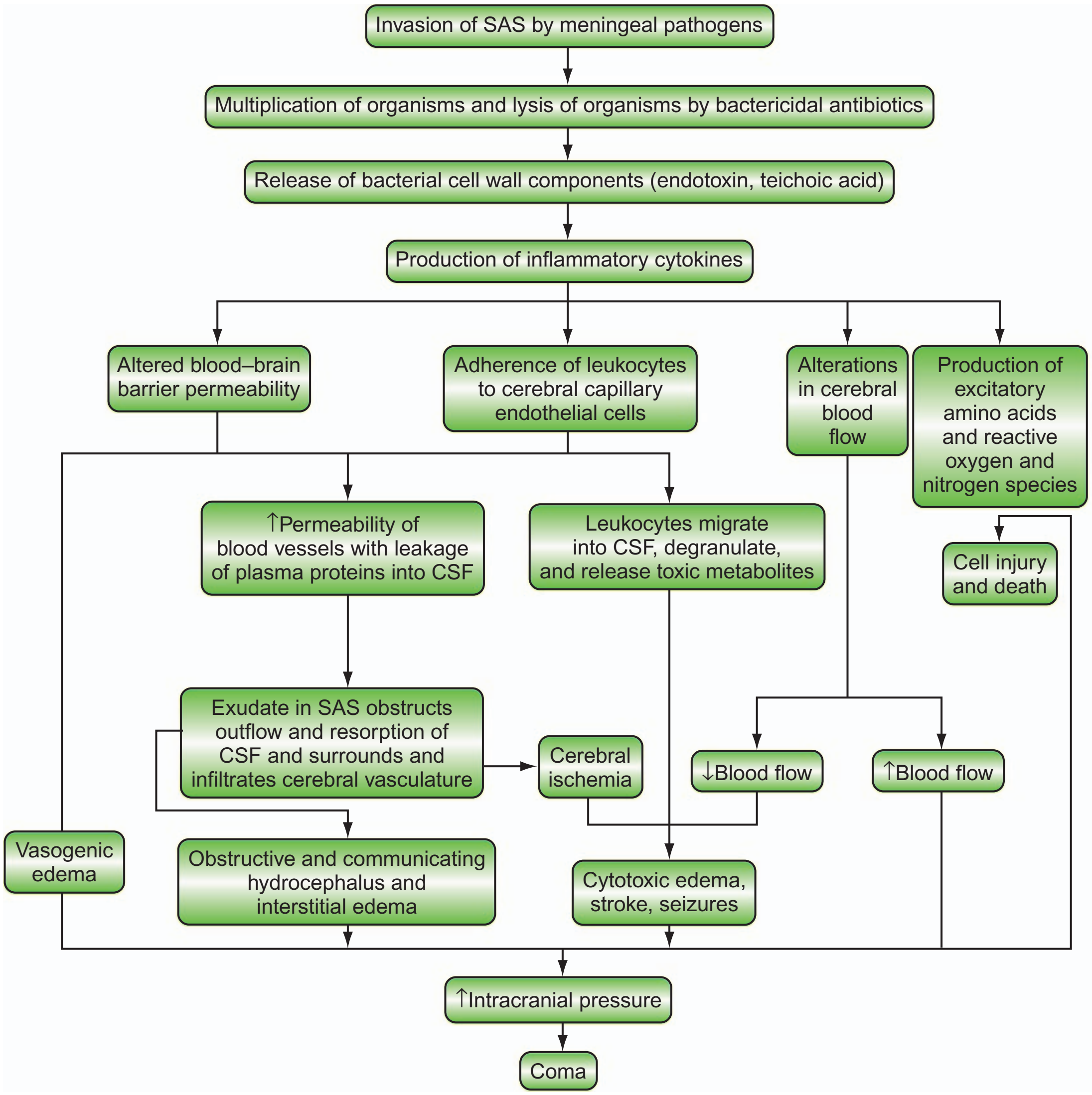
Invasion of SAS by meningeal pathogens
Multiplication of organisms and lysis of organisms by bactericidal antibiotics
Release of bacterial cell wall components (endotoxin, teichoic acid)
Production of inflammatory cytokines
Altered blood–brain barrier permeability
Adherence of leukocytes to cerebral capillary endothelial cells
Alterations in cerebral blood flow
Production of excitatory amino acids and reactive oxygen and nitrogen species
↑Permeability of blood vessels with leakage of plasma proteins into CSF
Leukocytes migrate into CSF, degranulate, and release toxic metabolites
Cell injury and death
Exudate in SAS obstructs outflow and resorption of CSF and surrounds and infiltrates cerebral vasculature
Cerebral ischemia
↓Blood flow
↑Blood flow
Vasogenic edema
Obstructive and communicating hydrocephalus and interstitial edema
Cytotoxic edema, stroke, seizures
↑Intracranial pressure
Coma

FIGURE 38-1 ■ Inflammatory cascade leading to the neurologic complications of bacterial meningitis. CSF, Cerebrospinal fluid; SAS, subarachnoid space. (Reprinted by permission of Karen L. Roos, MD, Indiana University Hospital, Indianapolis.)

plasma proteins into the CSF and further contributing to the inflammatory exudate in the subarachnoid space.

Dexamethasone exerts its beneficial effect by inhibiting the synthesis of IL-1 and TNF at the level of mRNA and through decreasing CSF outflow resistance and stabilizing the blood–brain barrier. The rationale for giving dexamethasone prior to antibiotic therapy is that dexamethasone inhibits the production of TNF if administered to macrophages and microglia before they are activated by endotoxin, both by diminishing the quantity of TNF mRNA in response to endotoxin and by preventing its translation. Dexamethasone is unable to regulate TNF production once induction occurs.

A meta-analysis of randomized, controlled trials of dexamethasone therapy in childhood bacterial meningitis published from 1988 to 1996 confirmed the benefit of dexamethasone for *H. influenzae* type b meningitis if begun with or before intravenous antibiotics and also suggested a beneficial effect for pneumococcal meningitis in children.[7] Maximal benefit from dexamethasone therapy is dependent on timing.

A common early criticism of the dexamethasone trials is that in the majority of cases, the causative organism of the meningitis was *H. influenzae* type b. However, this organism no longer is one of the more common etiologic agents of bacterial meningitis because of the success of the Hib conjugate vaccine. Present understanding of the molecular basis of the neurologic complications of bacterial meningitis, however, does not suggest that the pathophysiology of the neurologic complications varies with the meningeal pathogen, with the exception of how the microorganism gains access to the CNS.

In 2002, a prospective, randomized, double-blind, multicenter trial of dexamethasone in 301 patients with acute bacterial meningitis was published. *S. pneumoniae* was the causative organism in 37 percent of patients in the dexamethasone group and 44 percent of the placebo group. Among the patients with pneumococcal meningitis, 26 percent in the dexamethasone group had an unfavorable outcome, as compared with 52 percent in the placebo group.[8] After the introduction of nationwide dexamethasone therapy in adults with pneumococcal meningitis in the Netherlands, the case fatality rate declined from 30 to 20 percent; a total of 45 percent of cases of bacterial meningitis were pneumococcal.[9] In meningococcal meningitis, reduced rates of death and hearing loss have been reported with adjunctive dexamethasone.[10]

An additional concern regarding the use of dexamethasone in the treatment of bacterial meningitis is its effect on the penetration of antibiotics into the CSF. Meningeal inflammation appears to improve the penetration of vancomycin. By decreasing meningeal inflammation, dexamethasone could theoretically reduce the penetration of vancomycin into the CSF. However, in a prospective, randomized clinical trial of bactericidal activity against cephalosporin-resistant pneumococci in children with acute bacterial meningitis, vancomycin (60 mg/kg daily) reliably penetrated the CSF when the children were treated concomitantly with dexamethasone (0.6 mg/kg daily, divided into four doses for 4 days).[11] The third- and fourth-generation cephalosporins and rifampin penetrate the CSF extremely well, even in the presence of dexamethasone.

The American Academy of Pediatrics recommends the consideration of dexamethasone for bacterial meningitis in infants and children 6 weeks of age or older. The recommended dose is 0.6 mg/kg daily in four divided doses (0.15 mg/kg/dose) given intravenously for the first 4 days of antibiotic therapy. The first dose of dexamethasone should be administered 15 to 20 minutes before or at least with the first dose of antibiotics. Results of clinical trials of dexamethasone therapy in children have demonstrated its efficacy in decreasing meningeal inflammation and neurologic sequelae and in reducing the incidence of sensorineural hearing loss in bacterial meningitis from any cause.

The Infectious Diseases Society of America (IDSA) practice guidelines for the management of bacterial meningitis in adults recommend the use of dexamethasone with suspected or proven pneumococcal meningitis.[12] The recommended dose is 0.6 mg/kg daily in four divided doses for the first 4 days of antimicrobial therapy, with the first dose administered 15 to 20 minutes before or at least concomitant with the first dose of antibiotic. A favorable trend toward reduced rates of hearing loss and death with no evidence that dexamethasone is harmful has also been reported in patients with meningococcal meningitis.[10]

Prevention

It is recommended that college freshmen be vaccinated against meningococcal meningitis with the quadrivalent (A, C, W135, Y) meningococcal polysaccharide vaccine and with the serogroup B vaccine. During an outbreak of meningococcal disease, individuals who have not been previously vaccinated should be treated with chemoprophylaxis. Meningococcal disease can develop as quickly as within 2 to 5 days of presentation of the index case. Vaccination is not a substitute for chemoprophylaxis to prevent secondary disease, because there is an insufficient amount of time for development of the optimum effect of vaccination, which requires approximately 1 to 2 weeks for good antibody production. Adults and adolescents who have not been vaccinated but have been exposed to an individual with meningococcal disease can be treated with rifampin, 600 mg twice daily for 2 days. Children, older than age 2, can be treated with rifampin, 10 mg/kg twice daily for 2 days or a single injection of ceftriaxone 125 mg. Rifampin should not be used in pregnant women. Pregnant and lactating women and children under 2 years of age may be given intravenous or intramuscular ceftriaxone in a single injection of 250 mg for adults and 125 mg for children.

Vaccination against pneumococci is recommended for adults older than 65 years, adults with chronic underlying diseases (cardiopulmonary diseases, renal diseases, diabetes mellitus, splenectomy, and CSF fistula), and immunocompromised patients, including those infected with the human immunodeficiency virus (HIV).

BRAIN ABSCESS

A brain abscess is a focal suppurative infection in the brain parenchyma that typically begins as a localized area of cerebritis and develops into a collection of pus surrounded by a well-defined capsule. In a systematic review and meta-analysis of nearly 10,000 patients, brain abscess was found to develop from a contiguous suppurative focus of infection (e.g., frontoethmoidal sinusitis, chronic otitis media, mastoiditis, or meningitis) or hematogenous dissemination from a distant site of infection (e.g., lungs, skin, endocarditis, dental, or urinary tract infections) in the majority of patients.[13] Direct inoculation from head trauma or a neurosurgical procedure was a less common source. Nearly 20 percent of cases were polymicrobial, so overlap in the modes of dissemination was not uncommon. In another 20 percent of cases, no source of infection was identified. It should be noted that bacteria are not a common cause of brain abscess in immunosuppressed patients because of routine prophylaxis with antibiotics during episodes of neutropenia. The single exception to this is *Nocardia asteroides*, which is the causative organism in an increasing number of cases of brain abscess in patients with defects in cell-mediated immunity.

Etiology

The most common source of brain abscess is direct spread of infection from a contiguous suppurative focus of infection or hematogenous spread from a distant site of infection. Brain abscesses that arise from intracranial extension of paranasal sinus infections are caused usually by microaerophilic streptococci and anaerobic organisms (e.g., *Bacteroides* species, *Fusobacterium* species, and anaerobic streptococci), Enterobacteriaceae, and *Haemophilus* species. Bacterial infection in the paranasal sinuses spreads intracranially to the frontal or temporal lobe either by retrograde thrombophlebitis of the diploic veins or via a contiguous area of osteomyelitis. Brain abscesses associated with a dental procedure or dental abscesses are also typically due to microaerophilic streptococci and anaerobic organisms. A brain abscess may arise from direct extension of mastoid infection or via retrograde thrombophlebitis of the emissary veins within the temporal bone from mastoiditis. Middle ear infections can cause temporal lobe abscess by direct spread of infection through the tegmen antrum or petrous portion of the temporal bone. Brain abscesses that arise from middle ear infections are most often due to *Streptococcus* species, Enterobacteriaceae, *Bacteroides* species (including *B. fragilis*), and *P. aeruginosa*. A brain abscess may develop from hematogenous dissemination of microorganisms from a remote site of infection such as the heart, the lungs, the abdomen, or the urinary tract. Metastatic abscesses are often multiple and tend to form primarily in areas supplied by the middle cerebral artery (i.e., posterior frontal or parietal lobes) at the interface of gray and white matter, where capillary blood flow is slowest.

A common cause of brain abscess in infants and children is cyanotic congenital heart disease, with tetralogy of Fallot and transposition of the great vessels being the most frequent associated anomalies. As a general rule, a brain abscess in these patients develops only in an area of ischemic or devitalized brain tissue. Cyanotic congenital heart disease causes reduced rates of blood flow in the microcirculation of the brain resulting in hypoxia or infarction. Neonatal brain abscesses occur as a complication of meningitis, a predisposing condition that is uncommon in older children and adults; the most common causative organisms of bacterial brain abscess in neonates and infants are *Proteus* species and *Citrobacter* species. Brain abscess is an uncommon complication of neonatal group B streptococcal or *E. coli* meningitis.

When a brain abscess develops as a complication of penetrating head trauma, *S. aureus* is the most common pathogen found. Such abscesses are frequently multiloculated and may contain foreign bodies. A brain abscess following a neurosurgical procedure is typically due to staphylococci or gram-negative bacilli.

Clinical Presentation

Headache is the most common presenting complaint in patients with brain abscess, and fever occurs in fewer than 50 percent of patients. Up to 25 percent of patients present with new-onset focal or generalized seizures.[14] The findings on neurologic examination are related both to the site of the abscess and to the presence of increased ICP. Hemiparesis is a common localizing sign of a frontal or parietal lobe abscess. A temporal lobe abscess may be associated with dysphasia or a visual field deficit (e.g., upper homonymous quadrantanopia). A patient with a cerebellar abscess usually presents with nystagmus and ataxia. When the brain abscess is complicated by increased ICP, the clinical findings may include papilledema, deficits of the oculomotor (III) or abducens (VI) nerves, and an alteration in consciousness ranging from lethargy to irritability, confusion, or coma.

Diagnosis

Brain MRI is the best neuroimaging procedure for demonstrating a brain abscess, especially one that is in an early (i.e., cerebritis) stage. On T2-weighted images, cerebritis is evident as an area of hyperintensity. A mature brain abscess appears hypointense to CSF on T1-weighted sequences and demonstrates ring enhancement following administration of intravenous gadolinium. On T2-weighted images, a mature brain abscess has a central area of pus that is hyperintense, is surrounded by a well-defined hypointense capsule, and has a surrounding area of hyperintense edema. Diffusion-weighted MRI is helpful in differentiating a brain abscess from other types of cystic lesions as brain abscesses typically show restricted diffusion.

On contrast-enhanced CT, the mature abscess has the appearance of a low-density lesion with a sharply demarcated, dense ring of contrast enhancement surrounded by a variable hypodense region of edema. In both the early (i.e., cerebritis) and mature stages, a marginal ring of density is present on contrast-enhanced images; however, in the cerebritis stage, the enhancing ring forms an inhomogeneous "halo." As the abscess matures, its margin becomes more discrete and the associated enhancement more homogeneous. There may be leakage of contrast medium into the low-density center of an abscess in the cerebritis stage.

The etiologic organism of a brain abscess is determined by stereotactic needle aspiration. This procedure not only provides diagnostic specimens for Gram stain and culture but also permits therapeutic drainage of pus. Surgical resection can be considered for solitary abscesses that are superficial and not located in eloquent brain tissue. Lumbar puncture should be avoided in patients with known or suspected focal intracranial infections due to the danger of herniation and because the diagnostic yield is low. About 50 percent of patients with a brain abscess have a peripheral leukocytosis. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are elevated in the majority. Blood cultures should be drawn prior to initiation of empiric antimicrobial therapy, as a positive result is present in 25 to 50 percent of cases.

Differential Diagnosis

The differential diagnosis of a brain abscess includes focal structural or space-occupying lesions such as tumor, stroke, subdural empyema, and superior sagittal sinus thrombosis.

Treatment

Almost any brain abscess that measures greater than 1 cm in diameter can undergo stereotactic aspiration, regardless of location.[14] Antibiotic therapy is based on culture and sensitivity testing of the specific etiologic organism of the brain abscess. Empiric antibiotic therapy should be based on a knowledge of the organisms most frequently encountered with the suspected etiology of the brain abscess until the results of culture and sensitivity studies are available (Table 38-4).

Abscesses originating from the paranasal sinuses are caused predominantly by microaerophilic streptococci, anaerobic organisms (*Bacteroides* species, *Fusobacterium* species, and anaerobic streptococci), Enterobacteriaceae, and *Haemophilus* species. A combination of a third- or fourth-generation cephalosporin along with metronidazole is recommended for empiric therapy. The doses of these antimicrobial agents are provided in Table 38-2. A brain abscess associated with dental disease is treated with a combination of a third- or fourth-generation cephalosporin along with metronidazole to cover streptococci and *B. fragilis.* A brain abscess that complicates otitis media or mastoiditis may be caused by *Streptococcus* species, *Bacteroides* species (including *B. fragilis*), Enterobacteriaceae, or *P. aeruginosa.* A combination of metronidazole and ceftazidime or meropenem is recommended. Cerebral abscesses due to bacteremia from a pyogenic lung infection, urinary sepsis, or an intra-abdominal source of infection are treated with a combination of metronidazole and ceftazidime or meropenem until the results of culture and antimicrobial susceptibility tests are available. A brain abscess that develops in association with endocarditis is most often caused by *S. aureus* or microaerophilic streptococci; empiric therapy should include a combination of vancomycin plus a third- or fourth-generation cephalosporin (e.g., cefotaxime).

The most common organisms isolated when brain abscess complicates cyanotic congenital heart disease are *viridans* streptococci (microaerophilic streptococci), anaerobic streptococci, and occasionally *Haemophilus* species. A combination of cefotaxime plus metronidazole is recommended. Metronidazole has excellent bactericidal activity against strict anaerobes, adequate oral absorption, and good penetration into CSF and brain abscess cavities, but streptococci and aerotolerant anaerobes are resistant to metronidazole. Cefotaxime is added to cover *Haemophilus* species, and is the preferred third-generation cephalosporin because it and its lipophilic metabolite, desacetylcefotaxime, have

TABLE 38-4 ■ Etiologic Organisms of Brain Abscess and Empiric Therapy

Source	Organisms	Antibiotics
Paranasal sinuses	Microaerophilic streptococci *Bacteroides* species *Fusobacterium* species *Haemophilus* species Anaerobic streptococci *Staphylococcus aureus*	Third- or fourth-generation cephalosporin *plus* metronidazole *plus* vancomycin
Dental disease	Streptococci *Bacteroides fragilis*	Penicillin G *or* a third- or fourth-generation cephalosporin *plus* metronidazole
Otitis media or mastoiditis	*Streptococcus* species Enterobacteriaceae *Bacteroides* species (including *B. fragilis*) *Pseudomonas aeruginosa*	Metronidazole *plus* ceftazidime *or* meropenem
Pulmonary disease	*Streptococcus* species *Actinomyces* species *Fusobacterium* species	Metronidazole *plus* ceftazidime *or* meropenem
Endocarditis	*Staphylococcus aureus* Microaerophilic streptococci	Vancomycin *plus* cefotaxime
Intra-abdominal site	*Streptococcus* species Enterobacteriaceae Anaerobes	Metronidazole *plus* ceftazidime *or* meropenem
Urinary tract	*Pseudomonas* species Enterobacteriaceae	Metronidazole *plus* ceftazidime *or* meropenem
Cyanotic congenital heart disease	Anaerobic and microaerophilic streptococci (*viridans* streptococci)	Penicillin G *plus* cefotaxime *plus* metronidazole
Neonatal meningitis	*Proteus* species *Citrobacter* species	Ampicillin *plus* aminoglycoside *or* cefotaxime
Immunosuppressed state	*Nocardia asteroides* *Clostridium* species *Pseudomonas aeruginosa* *Xanthomonas maltophilia* *Enterobacter cloacae* Staphylococci Gram-negative bacilli	Trimethoprim-sulfamethoxazole *plus* ceftazidime *or* meropenem *plus* vancomycin
Penetrating head injury	Staphylococci Gram-negative bacilli Anaerobes	Vancomycin *plus* ceftazidime *or* meropenem *plus* metronidazole
Neurosurgical procedure	Staphylococci Gram-negative organisms Enterobacteriaceae *Pseudomonas aeruginosa*	Vancomycin *plus* ceftazidime *or* meropenem

excellent antibacterial activity and penetrate and accumulate within abscess cavities.

Brain abscesses complicating neurosurgical procedures are usually due to staphylococci or gram-negative organisms. Empiric therapy should be a combination of vancomycin plus ceftazidime, cefepime, or meropenem. The most common pathogens recovered from brain abscesses that complicate penetrating head injuries are staphylococci and gram-negative bacteria, but anaerobes and *Nocardia* species may also be found. Empiric therapy should include a combination of vancomycin, ceftazidime, and metronidazole.

Brain abscesses are treated with a 6- to 8-week course of parenteral antimicrobial therapy. During treatment, MRI can be performed every 2 weeks for 3 months or until clinical recovery is evident and should also be undertaken at any sign of clinical deterioration. If the abscess cavity is still visible on MRI following completion of parenteral antibiotics, oral antibiotics should be initiated and continued until there is complete resolution of the cavity on neuroimaging.

The majority of abscesses can be managed with stereotactic aspiration and therapeutic drainage in combination with antimicrobial therapy, with two exceptions. An abscess that is in the cerebritis stage and has not become encapsulated may respond to antimicrobial therapy alone. Brain abscesses due to *N. asteroides* usually require more extensive surgical excision and therapy with trimethoprim-sulfamethoxazole.

Corticosteroids are recommended only for those patients with significant cerebral edema and associated mass effect causing increased ICP. Corticosteroids should not be given routinely to patients with brain abscesses, as they delay the encapsulation of the abscess.

The use of prophylactic anticonvulsant therapy during the course of antimicrobial therapy is controversial. The risk for focal or generalized seizures is of concern. However, more recent studies do not show a decreased seizure rate with prophylactic treatment, and therefore, prophylactic treatment is now not routinely recommended in patients with brain abscess.[14] If seizures do occur, it is recommended to continue anticonvulsant treatment until resolution of abscess on neuroimaging, at which time tapering off of anticonvulsants can be attempted.

SUBDURAL EMPYEMA AND CRANIAL EPIDURAL ABSCESS

A subdural empyema is a collection of pus in the space between the dura and the arachnoid (Fig. 38-2).

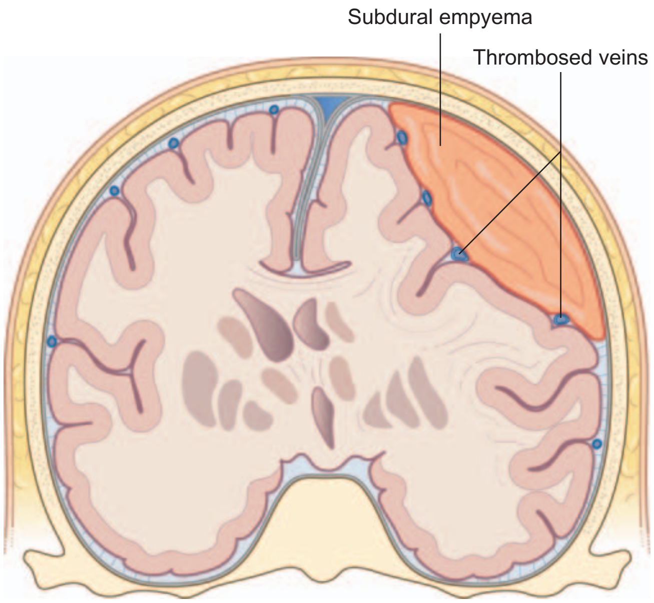

FIGURE 38-2 ■ Schematic appearance of a subdural empyema.

A cranial epidural abscess develops in the space between the dura and the inner table of the skull (Fig. 38-3). A subdural empyema is a more malignant and life-threatening infection than is a cranial epidural abscess.

Etiology

Paranasal sinusitis, especially frontal sinusitis, is the most common predisposing condition for subdural empyema. Septic thrombophlebitis of the mucosal veins of the sinuses results in retrograde extension of infection with drainage of bacteria into the dural venous sinuses and cortical veins and the formation of a subdural empyema. Subdural empyema may also result from direct infection of the subdural space during a neurosurgical procedure such as drainage of a subdural hematoma; as a complication of head trauma; or from infection of a subdural effusion. It only rarely develops from hematogenous dissemination of bacteria from a distant focus of infection.

A cranial epidural abscess may develop as a complication of a craniotomy or a compound skull fracture or as the result of spread of infection from the frontal sinuses, middle ear, mastoid, or orbit. When an epidural abscess develops as a complication of a craniotomy, it is either from direct infection of the epidural space or as a complication of a contiguous area of osteomyelitis that develops from infection of a wound or bone flap. A cranial epidural abscess rarely results from hematogenous seeding of the epidural space from a distant site of infection.

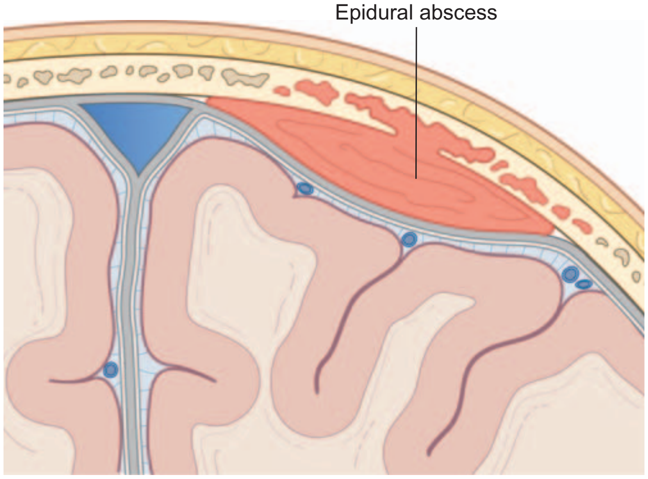

FIGURE 38-3 ■ Cranial epidural abscess located in the space between the dura and the inner table of the skull.

Aerobic and microaerophilic streptococci and anaerobic bacteria are the most common causative organisms of subdural empyema or epidural abscess that develops as a complication of sinusitis, middle ear infection, or mastoiditis. A subdural empyema or an epidural abscess that develops as a complication of craniotomy, compound skull fracture, or drainage of a subdural hematoma is usually caused by *S. aureus*, coagulase-negative staphylococci, or gram-negative organisms. A subdural effusion may be a complication of bacterial meningitis in infants and children. It is typically a self-limited process that resolves as the meningitis is treated. Occasionally, a subdural effusion may become infected, causing a subdural empyema—the causative organism is the organism responsible for the meningitis.

Clinical Presentation

Headache is the most common complaint with a subdural empyema and is initially localized to the side of the subdural infection. It may be accompanied by fever and symptoms of sinusitis or otitis media. The evolution of a subdural empyema tends to be remarkably rapid. There are no septations in the subdural space, and, as a result, the purulent exudate can spread quite extensively. The headache may become more severe and generalized as the infection spreads. Focal neurologic deficits or seizures may also occur. Contralateral hemiparesis or hemiplegia is the most common focal neurologic deficit. Seizures begin as focal motor type that then may become secondarily generalized. Over the course of a few days, the level of consciousness decreases from somnolence to stupor and finally to coma.[15] In a review of subdural empyema arising from sinusitis in 18 patients, headache was present in 15 patients (83%), fever in 17 patients (94%), focal neurologic signs in 17 patients (94%), nuchal rigidity in 14 patients (78%), altered level of consciousness in 10 patients (56%), seizures in 10 patients (56%), and sinus tenderness or periorbital swelling in 7 patients (39%).[15]

The clinical presentation of a cranial epidural abscess is distinctly different from that of a subdural empyema. The patient is not as ill, and there is rarely rigidity of the neck or focal neurologic signs.[15] Presentation is typically with an unrelenting hemicranial headache accompanied by persistent fever. Focal neurologic deficits, seizures, and signs of increased ICP do not typically develop until the infection spreads into the subdural space (i.e., becomes a subdural empyema).

Diagnosis

Cranial MRI is the procedure of choice for demonstrating these lesions because it is free from bony artifacts adjacent to the inner table of the skull and readily can demonstrate extracerebral fluid collections. T1-weighted postgadolinium and T2-weighted sequences are best for demonstrating subdural empyema or cranial epidural abscess. Subdural empyema is hyperintense on T1-weighted sequences. There is contrast enhancement of the rim of the empyema separating the empyema from the subjacent brain parenchyma. The empyema itself appears as a crescent-shaped lesion of hyperintensity on T2-weighted sequences.

On T1-weighted sequences, an epidural abscess has a signal intensity that is between that of normal brain parenchyma and CSF. Enhancement of the dura is seen on T1-weighted contrast-enhanced images. An epidural abscess appears as a lentiform or crescentic purulent fluid collection that is hyperintense on T2-weighted sequences.

Lumbar puncture should not be performed in patients with subdural empyema or epidural abscess. The etiologic organism is identified by Gram stain and culture of pus obtained either via burr hole or by craniotomy.

Treatment

Immediate neurosurgical drainage of a subdural empyema or a cranial epidural abscess is the definitive step in their management. At surgery, Gram stain and culture of the purulent material are performed. Empiric antimicrobial therapy pending the results of Gram stain and culture should cover aerobic and microaerophilic streptococci, anaerobic bacteria, staphylococci, and gram-negative bacilli and include a combination of a third- or fourth-generation cephalosporin (e.g., ceftriaxone, cefotaxime, or cefepime), metronidazole, and vancomycin. Ceftazidime or meropenem should be substituted for cefotaxime or ceftriaxone in neurosurgical patients because of better *Pseudomonas* species coverage. Antibiotics can be modified when the results of Gram stain and bacterial culture and sensitivity testing are known. A 4-week course of intravenous antibiotic therapy is recommended for subdural empyema, followed by a 2-week course of oral antibiotic therapy. A cranial epidural abscess is treated for 3 weeks with parenteral antibiotics in the absence of osteomyelitis, and for 6 to 8 weeks when it is a complication of a contiguous area of osteomyelitis.

SPINAL EPIDURAL ABSCESS

An epidural abscess may develop in the spinal epidural space (Fig. 38-4). The most common locations are either the posterior midthoracic region between the fourth and the eighth thoracic vertebrae (Fig. 38-5) or the lower lumbar epidural space. Anterior abscesses occur less often than do posterior abscesses and usually occur at the cervical level.

Etiology

A spinal epidural abscess develops in the space outside the dura mater but within the spinal canal as the result of hematogenous spread of bacteria from a remote site of infection to the epidural space (e.g., secondary to skin infection, urinary tract infection, intra-abdominal infection, pelvic inflammatory disease, pneumonia, endocarditis, or infections from intravenous lines); by direct extension from a contiguous infection (e.g., an area of osteomyelitis in an adjacent vertebral body); by direct infection of the epidural space during spine surgery or epidural anesthesia; or by direct extension of infection from decubitus ulcers, infected abdominal

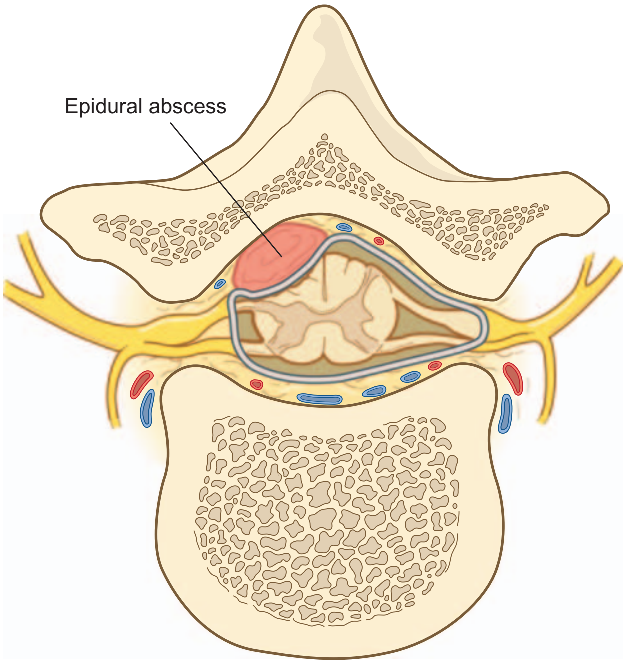

FIGURE 38-4 ■ An abscess in the epidural space posterior to the spinal cord.

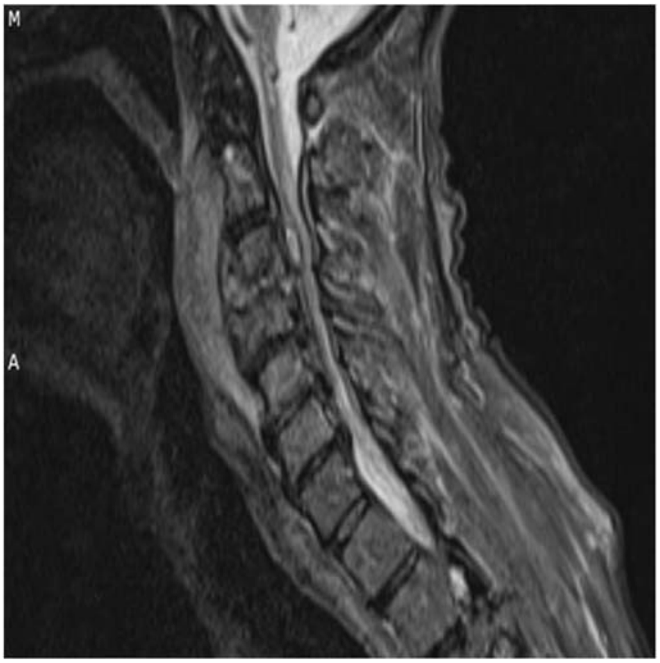

FIGURE 38-5 ■ Sagittal T2-weighted magnetic resonance imaging of the cervical spine demonstrating an epidural fluid collection (abscess) compressing the spinal cord.

wounds, retropharyngeal abscesses, or psoas muscle abscesses. Immunosuppression from chronic disease (such as diabetes or chronic renal insufficiency), HIV infection, corticosteroid therapy, and immunosuppressive therapies are increasingly reported as predisposing conditions.

The etiologic organism of the spinal epidural abscess is predictable from the predisposing condition. A spinal epidural abscess that arises from hematogenous dissemination from a skin infection or contamination of intravenous lines, or as a complication of spine surgery or epidural anesthesia, is caused in the majority of cases by *S. aureus*. Infection that reaches the epidural space by hematogenous spread of bacteria from a genitourinary infection or intra-abdominal infection to the paravertebral venous plexus is usually caused by gram-negative bacilli.

Clinical Presentation

Patients with a bacterial spinal epidural abscess present with a classic neurologic syndrome. Back pain is the initial symptom, followed within 2 to 3 days by radicular pain in the extremities or pain in an intercostal thoracic dermatomal distribution. As the disease progresses, weakness of appendicular muscles is associated with decreased sensation below the level of the lesion and loss of bowel and bladder control. Finally, there is complete paralysis of appendicular muscles and loss of all sensory modalities below the level of the lesion (i.e., a sensory level). The majority of patients also have an elevated temperature.

The possibility of a spinal epidural abscess should be considered in any patient with fever, back pain (especially with focal vertebral pain and tenderness), and radicular pain in the extremities or pain in a thoracic dermatomal distribution.

Diagnosis

Gadolinium-enhanced MRI is the diagnostic procedure of choice for spinal epidural abscess. MRI of the thoracic and lumbar region should be obtained to visualize the extent of the epidural abscess, and it is reasonable to obtain images of the cervical region as well, especially if the upper extremities are involved. A lumbar puncture should not be performed at the site of a possible abscess because of the risk of spread of infection from the epidural to the subarachnoid space. The majority of patients have an elevated peripheral white blood cell count, and blood cultures may demonstrate the organism.

Treatment

A spinal epidural abscess is treated with immediate laminectomy for decompression and drainage of the epidural space. Empiric therapy depends on the predisposing condition. Because *S. aureus* is the most common etiologic agent, and given the increasing incidence of community- and hospital-acquired methicillin-resistant *S. aureus*, empiric therapy should include vancomycin in addition to a third- or fourth-generation cephalosporin. In the postneurosurgical patient, ceftazidime (instead of ceftriaxone) or meropenem should be added to the empiric regimen to cover gram-negative bacilli. When a spinal epidural abscess is the result of local extension from an adjacent infection, such as a decubitus ulcer, empiric therapy should cover *S. aureus* and gram-negative bacilli. If the source is an abdominal infection, anaerobic coverage with metronidazole should be added. Once a specific organism has been isolated, the antibiotic regimen can be modified based on the results of sensitivity studies. The duration of intravenous antibiotic therapy is typically at least 6 weeks when the spinal epidural abscess is associated with vertebral osteomyelitis. If osteomyelitis is not present, intravenous antibiotic therapy is usually continued for 3 to 4 weeks.[16]

Prognosis is dependent on the mechanism of spinal cord injury. If the abscess is due to compression of the arterial blood supply, arterial or venous thrombosis, or septic thrombophlebitis, the outcomes are frequently poor. If the mechanism is spinal cord compression (the neurosurgeon will see pulsation of the spinal cord after decompression), outcomes are excellent if laminectomy is performed early in the course of the abscess, especially if the patient has back pain alone or back pain and radicular symptoms. If the patient is paretic (but not plegic) prior to surgery, the expectation is either no weakness or a lesser degree of weakness postoperatively. If the patient is plegic, some improvement is expected postoperatively if the surgery occurs within 36 hours of paralysis.[16]

SEPTIC INTRACRANIAL THROMBOPHLEBITIS

Septic intracranial thrombophlebitis is a bacterial infection of the cortical veins and sinuses with resultant venous thrombosis. It is a complication of bacterial meningitis, subdural empyema, epidural abscess, or infection in the skin of the face, paranasal sinuses, middle ear, or mastoid. Textbooks tend to treat septic intracranial thrombophlebitis as a distinct entity, but in reality clinicians probably underdiagnose it as it usually appears as a complication of bacterial meningitis or subdural empyema. The availability of noninvasive neuroimaging procedures, such as magnetic resonance venography and CT angiography, that demonstrate dural sinus thrombosis may increase the recognition of this complication.

Etiology

The superior sagittal sinus is the largest of the venous sinuses (Fig. 38-6), and it receives blood from the frontal, parietal, and occipital superior cerebral veins and the diploic veins, which communicate with the meningeal veins. Infection can spread from the meninges to the superior sagittal sinus via the diploic veins, especially in cases with purulent exudate near the superior sagittal sinus. The cerebral veins and venous sinuses have no valves; therefore, blood within them can flow in either direction. The superior sagittal sinus drains into the transverse sinus. The transverse sinuses also receive venous drainage from small veins

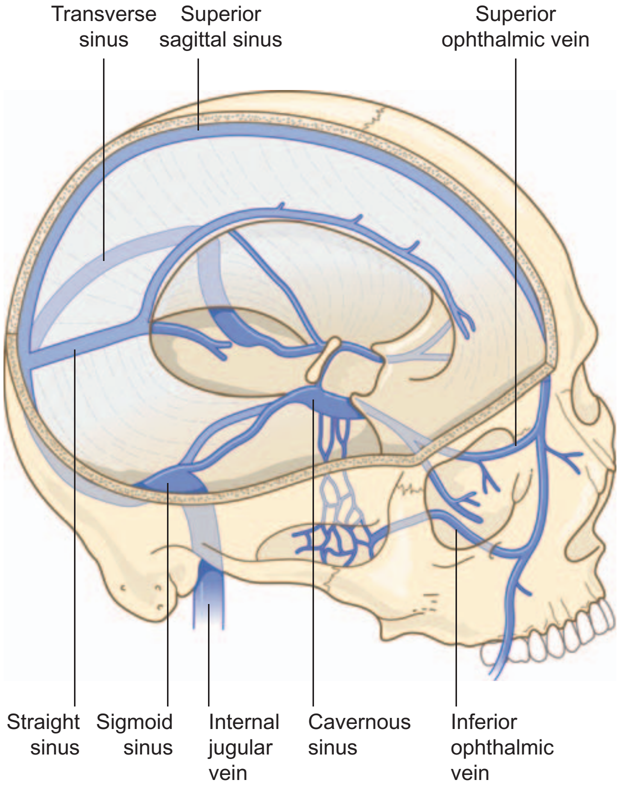

FIGURE 38-6 ■ The major cerebral venous sinuses.

from both the middle ear and the mastoid cells. The transverse sinus becomes the sigmoid sinus before draining into the internal jugular vein. Septic transverse or sigmoid sinus thrombosis can be a complication of acute and chronic otitis media or mastoiditis. Infection spreads from the mastoid air cells to the transverse sinus via the emissary veins or by direct invasion.

The cavernous sinuses are inferior to the superior sagittal sinus at the base of the skull (Fig. 38-6). Bacteria in the sphenoid and ethmoid sinuses can spread to the cavernous sinuses via the small emissary veins, causing septic cavernous sinus thrombosis.

Dehydration from vomiting and hypercoagulable states contribute to the formation of thrombosis in the cerebral venous sinuses. Immunologic abnormalities, including the presence of circulating antiphospholipid antibodies, can also serve as risk factors. Thrombosis of a dural sinus can be associated with thrombosis of the cortical veins that drain blood into and out of the sinuses, resulting in small parenchymal hemorrhages.

Clinical Presentation

Patients with septic thrombosis of the superior sagittal sinus have headache, nausea and vomiting, weakness of the lower extremities with bilateral Babinski signs, focal or generalized seizures, and an alteration in the level of consciousness. There may be a rapid development of stupor and coma.

The signs and symptoms of septic cavernous sinus thrombosis are fever, headache, and diplopia. The oculomotor nerve (III), trochlear nerve (IV), abducens nerve (VI), and ophthalmic and maxillary branches of the trigeminal nerve (V) all pass through the cavernous sinus; therefore, the classic signs of a septic cavernous sinus thrombosis are ptosis, proptosis, and extraocular dysmotility due to deficits of cranial nerves III, IV, and VI. Hypo- or hyperesthesia of the ophthalmic and maxillary divisions of the fifth cranial nerve and a decreased corneal reflex may be detected.

Patients with septic transverse sinus thrombosis may present with Gradenigo syndrome, which is characterized by otitis media, VI nerve palsy, and retro-orbital or facial pain.

Diagnosis

The diagnosis of septic venous sinus thrombosis is suggested by an absent flow void within the sinus on MRI and is confirmed by magnetic resonance venography, CT angiography, or the venous phase of cerebral angiography.

Treatment

Septic venous sinus thrombosis has traditionally been treated with antibiotics and hydration along with removal of infected tissue and thrombus. Anticoagulation with dose-adjusted heparin is reported to be beneficial in patients with aseptic venous sinus thrombosis and is used in the treatment of septic venous sinus thrombosis when patients are worsening despite antimicrobial therapy and intravenous fluids. Occasionally good clinical results have been reported with catheter-directed urokinase therapy and intrathrombus infusion of recombinant tissue plasminogen activator for aseptic venous sinus thrombosis that clinically progresses while on anticoagulation, but there has not been enough experience with these therapies for septic venous sinus thrombosis to make recommendations regarding their use. In patients with bacterial meningitis and lower extremity weakness or a decreased level of consciousness, the use of noninvasive magnetic resonance venography and CT angiography may increase the recognition of this complication.

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CHAPTER

39

Spirochetal Infections of the Nervous System

JOHN J. HALPERIN

SYPHILIS
- Background
- Diagnosis
- Clinical Features
- Treatment

LYME DISEASE
- Background
- Clinical Features
  - *General*
  - *Neuroborreliosis*
- Diagnosis
- Treatment and Outcome

Spirochetes cause a broad range of human illnesses, including relapsing fever, yaws, pinta, leptospirosis, and periodontal disease. Although leptospirosis and relapsing fevers can cause severe headaches and myalgias in conjunction with high fever and severe systemic illness, two spirochetal infections target the nervous system specifically: syphilis and Lyme disease. Both are the subject of popular mythology and have been blamed for far more than they could possibly have done. Syphilis swept Europe at a time when medicine had yet to understand such fundamental concepts as the germ basis of infection. Even early in the twentieth century, preeminent physicians referred to syphilis as the great imitator. Notably at that time, little was understood about cerebrovascular disease or other neurologic disorders. As late as the 1950s and beyond, anecdotal reports appeared about neurosyphilis having been diagnosed on the basis of silver stains of brain tissue—a highly problematic methodology since fibrillar structures normally present in the brain stain with silver and have a corkscrew-like appearance.

Similarly, Lyme disease has been blamed for innumerable “quality-of-life” ailments. At a time when science has sequenced the human genome, can detect subtle structural abnormalities with magnetic resonance imaging (MRI), and has developed an immense and powerful pharmacopoeia, many find it difficult to accept that medicine has limitations and, in particular, cannot provide simple biologic answers to and remedies for a constellation of common and distressing symptoms, variably known over the years by terms such as *neurasthenia*, *chronic fatigue syndrome*, and *fibromyalgia*, among others. In this setting, some have chosen to extrapolate from the known phenomenology of Lyme disease, emphasizing the areas of similarity between these symptom complexes and Lyme disease and ignoring the far more glaring differences.

There are fascinating similarities between syphilis and Lyme disease that deserve emphasis, as they presumably reflect basic biologic properties of spirochetes. Both infections can be chronic, despite the presence of easily demonstrable antibodies targeted against major epitopes. Presumably, this relates to the spirochetal predisposition to present a limited range of surface antigens, and then change the expressed epitopes over time, as conditions require. Both disorders are spread almost exclusively by intimate contact with a vector, reflecting the very limited ability of spirochetes to survive in vitro. Both begin with prominent, angry-looking cutaneous abnormalities that are surprisingly painless, the lack of pain presumably reflecting the peculiarities of the limited local host immune response.

Both disseminate widely and rapidly, easily broaching the blood−brain barrier, probably reflecting their own inherent motility and adherence to cell-surface molecules. Both seed the nervous system frequently but cause neurologic disease only in a subset of those seeded. Most important, both remain sensitive to fairly simple antibiotics. Although both are frequently described as

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presenting with protean manifestations, this reflects an approach to neurology based on phenomenology rather than pathophysiology. In fact, each infection usually causes a characteristic range of disorders. Specific manifestations in any given individual depend on the part of the nervous system involved, but the disorders are pathophysiologically related.

SYPHILIS

Background

Syphilis, caused by *Treponema pallidum*, became prominent in Europe shortly after the return of Columbus from the New World. Known at the time (in some circles) as "the French pox," the mode of transmission was recognized early on. The *Breviary of Health* of 1547 states clearly that "specially it is taken when one pocky person doth synne in lechery the one with another."[1] At that time, as with other newly introduced infectious diseases, the morbidity and mortality associated with syphilis were high. Then, presumably as the most susceptible hosts died and the bacteria self-selected for strains that could persist without killing or incapacitating their hosts, the bacteria and humankind settled into their current symbiotic relationship. Currently, there are about 31,000 cases of primary and secondary syphilis each year in the United States,[2] similar to the number of cases of Lyme disease confirmed by the Centers for Disease Control and Prevention (CDC).

Diagnosis

Diagnosis was originally clinical and rested on recognition of the characteristic chancre—a painless, ulcerated, indurated lesion at the site of primary infection that typically heals spontaneously. The lesion contains numerous spirochetes; one of the best methods of diagnosis is to scrape the lesion, place the scrapings in saline on a slide, and view the motile spirochetes with a dark-field microscope. In patients not seen at the time of the chancre, diagnosis initially rested on the recognition of one of the large number of clinical syndromes attributed to this disease.

More accurate diagnosis of later disease required advancements in laboratory techniques. Identification of the causative organism was an important first step, but diagnosis by culturing *T. pallidum* remains essentially impossible. The organism can be propagated by inoculation into susceptible animals but not cultured in vitro—hence the microbiologic approach traditionally used in clinical diagnosis of other bacterial infections is not useful.

The spirochete has now been very well characterized. Its length varies from 6 to 20 μm; its diameter is about 0.18 μm. It is shaped in a regular helix and exhibits corkscrew motility, propelled by its flagella. Its entire genome has now been sequenced. Despite this intimate knowledge of the spirochete, laboratory confirmation of infection, particularly after resolution of the chancre, remains dependent on serologic tests. These fall into one of two groups. Historically, screening has used nontreponemal tests, measuring "reaginic" antibodies—in essence, anticardiolipin antibodies. The reason that patients with this infection have high titers of anticardiolipin antibody remains unknown, but presumably reflects an interaction of the spirochete with host lipoproteins and other lipids.[3] Tests such as the Wasserman reaction, rapid plasma reagin (RPR), Venereal Disease Research Laboratory (VDRL), and Hinton tests all fall into this group. These tests have been thought to have very high sensitivity but, as indirect measures of infection, lack specificity. Patients with positive nontreponemal tests would then be further tested for specific antitreponemal antibodies, using the FTA-Abs (fluorescent treponemal antibody, absorbed against nonpathogenic treponemata to decrease cross-reactivity), the MHA-TP test (microhemagglutination for *T. pallidum*), or capture enzyme-linked immunosorbent (ELISA) or chemoluminescent assays (CIA).

Studies using CIAs or ELISAs for comparison suggest that reaginic tests are less sensitive than previously believed, leading to recommendations by some that direct tests be used for initial screening. Although the CDC still recommends the traditional sequence, it now also endorses the reverse sequence. In this approach the initial diagnosis starts with a specific treponemal test (ELISA or CIA), confirming positives with a nontreponemal test; discordant results are then further tested with a different specific treponemal test. To make matters even more confusing the European equivalent to the CDC recommends a different reverse approach, also starting with a specific treponemal test, but then confirming positives with a different specific test, testing discordant results with a nontreponemal test. Arguments in favor of each approach are based on assessments of positive and negative predictive values. Notably, a large study suggests that overall, both reverse approaches are equivalent,[4] although increasing evidence suggests the traditional method, starting with nontreponemal tests, is less sensitive.

Response to therapy is generally assessed by measuring titers of reaginic antibody. Typically, the serum titer in a VDRL or similar test declines steadily after successful treatment and eventually becomes negative in most cases, unlike specific assays, which remain positive indefinitely.

When serologic testing was introduced early in the twentieth century, seroprevalence rates of 8 to 14 percent were reported in major cities. It was at that time that the medical literature blossomed, attributing all manner of disease to syphilis. It may well be that at least some of this was misattribution due to coincidentally positive serologic tests, much as occurs in Lyme disease–endemic areas today (where, coincidentally, seroprevalence rates of 5 to 15% are common).

Diagnosis of nervous system disease relies heavily on examination of the cerebrospinal fluid (CSF), which is recommended in the assessment of any patient with primary or secondary syphilis and clinical suspicion of central nervous system (CNS) involvement or with tertiary syphilis. Invasion and infection of the CNS typically result in increased protein concentration or a CSF pleocytosis, with an increased proportion of B cells. Rarely there is mild hypoglycorrhachia. Active disease typically results in the presence of reaginic antibodies (VDRL) in the CSF. Chronic infection and stimulation of the immune response within the CNS generally result in increased CSF IgG concentration as well as production of oligoclonal bands. Synthesis of specific anti-*T. pallidum* antibody can often be demonstrated in the CSF. Interestingly, active infection leads to increased CSF concentration of CXCL13, a B cell–attracting cytokine, just as in nervous system Lyme disease.[5] Successful treatment usually leads to resolution of the CSF pleocytosis, with normalization of CSF protein, IgG concentration, CXCL13, and, usually, VDRL.

CSF-based diagnosis is usually straightforward but can sometimes be problematic, as reviewed elsewhere.[6] The CSF VDRL is considered highly specific—a positive CSF VDRL result is regarded as diagnostic of CNS syphilis. (The CSF RPR test has far more false-positive results.) The VDRL's specificity is probably related to the fact that the methodology is rather insensitive—a fairly high concentration of antibody is needed for the test to be judged positive. Thus, the presence of a positive VDRL in the CSF is unlikely to be an artifact of contamination of CSF with peripheral blood immunoglobulin. One potential diagnostic problem arises, however, in that although the CSF VDRL typically declines after successful treatment, it may remain positive for an extended period of time. In this circumstance, the return of the CSF white blood cell count and protein concentration to normal is usually taken as evidence of adequate treatment.

With the technically more sensitive methods used to detect antitreponemal antibodies (FTA-Abs, MHA-TP, ELISA, CIA), contamination is a more important issue. False-positive results can occur for one of at least three reasons. Antibodies against antigenically similar organisms (e.g., *Borrelia burgdorferi*) can cross-react. More important, if the lumbar puncture is traumatic, peripheral blood can contaminate the specimen, resulting in artifactual elevations in antibody titers. Probably most important, however, is the fact that some peripheral blood immunoglobulin always filters into the CSF. In the absence of CNS inflammation, there is minimal if any intrinsic production of antibodies within the CNS. However, CSF IgG concentration is typically 2 to 3 mg/dL, approximately 0.2 percent of peripheral blood IgG concentration, representing the small amount of serum immunoglobulin that normally passes through the blood–brain barrier. Just as in testing CSF Lyme serologies, standard testing conditions (diluting CSF 1:5 for the FTA-Abs, for example) are selected to compensate for this leakage. However, artifacts may arise in two important circumstances. In patients with high serum FTA-Abs titers, CSF titers may be positive simply by virtue of the small amount of specific antibody that normally filters in. Second, in the presence either of CNS inflammation or of blood–brain barrier breakdown for other reasons, the amount of peripheral blood immunoglobulin leaking into the CNS may be greater than assumed, resulting in an apparent increase in the concentration of the tested antibody but actually simply reflecting an overall and nonspecific increase in all antibody levels. These considerations notwithstanding, the CSF FTA is a highly sensitive if not entirely specific marker of neurosyphilis.

The absence of an absolute "gold standard" test for the diagnosis of neurosyphilis has resulted in controversy, differing recommendations for diagnostic strategies, and varying estimates of the sensitivity and specificity of different CSF tests. Whereas the CSF VDRL test is often said to be 100 percent specific, estimates of its sensitivity vary widely, depending on the alternative criteria used to define neurosyphilis. Screening CSF samples using the FTA-Abs and considering patients to have probable neurosyphilis if they have (1) a positive CSF FTA-Abs result, (2) a consistent clinical syndrome, and (3) elevation in either the CSF cell count, protein concentration, or both, leads to an estimated sensitivity of the CSF VDRL of 27 percent. Performing a similar analysis, but using the CSF MHA-TP as the primary criterion and comparing the CSF MHA-TP, CSF FTA-Abs, and CSF VDRL, suggests that the sensitivity of the CSF VDRL is about 40 percent, but that of the CSF MHA-TP is substantially greater than that of the FTA-Abs. However, there is evidence that as many as one-third of human immunodeficiency virus (HIV)–seronegative individuals with positive serum VDRL results will have inflammatory changes in the CSF, but no serologic (CSF VDRL or FTA-Abs) evidence of neurosyphilis, calling into doubt the assumptions underlying the first two conclusions.

Theoretically, a more definitive approach would be to determine whether antibodies targeted against *T. pallidum* are actually being produced within the CNS. Although a variety of techniques can be used, conceptually this is accomplished by measuring the antibody concentration in CSF and serum, normalizing for the relative total immunoglobulin concentrations in both, and determining whether specific antibody is disproportionately represented in the CSF. This approach, used in many other infections, should have very high specificity, although, again, sensitivity is difficult to define. Despite the intuitive appeal of this approach, sensitivity estimates have varied widely, depending on underlying assumptions, making its applicability uncertain at this time.

Clinical Features

After initial inoculation of spirochetes, the organism disseminates rapidly. Within weeks of infection the chancre develops at the site of infection. Chancres contain large numbers of spirochetes and are highly infectious. Untreated, they typically subside spontaneously over weeks. This early, localized disease constitutes primary syphilis. Over the ensuing few months, spirochetes disseminate, setting the stage for secondary syphilis. In this phase, there is a high antigen load, often with a significant spirochetemia. Spirochetes can invade any organ of the body but have a particular predilection for the skin (with secondary lesions, particularly involving the palms and soles), lymph nodes (particularly the epitrochlear nodes), kidney (with an immune complex–mediated glomerulonephritis), and CNS (seeded in between 25 and 40% of infected individuals). As many as 40 percent of untreated patients develop a lymphocytic meningitis. As in other basilar meningitides, the cranial nerves, particularly II to VIII, can be compromised. Intracranial pressure may be increased.

The disease then typically enters a latent phase, during which infection—and the immune response to it—persist. In the majority, the host immune response clears the infection. In a subset, late or tertiary complications develop. In some, this consists of disseminated granulomata, known as gummas, that can occur anywhere in the body, causing focal symptoms depending on location. Patients may develop gummas in the brain, causing local structural damage and symptoms. Gummas tend to be relatively benign but can be confused with neoplasms or other processes. Some patients develop an endarteritis obliterans affecting the vasa vasorum of the ascending aorta, causing characteristic aneurysmal dilatation.

Although neurologic involvement is generally divided into early or late (secondary or tertiary) manifestations, there is some variability in how different pathophysiologic entities are grouped. The acute meningitis, with or without cranial nerve involvement, typically occurs during acute spirochetal dissemination and is considered part of secondary (acute disseminated) disease. All other manifestations occur later in the disease, in what might be termed *late disseminated infection* ("tertiary syphilis"), although some tend to occur earlier in this "late" phase, others later.

Symptomatic nervous system involvement ultimately occurs in 4 to 6 percent of untreated patients and tends to take one of several forms. One of the earlier occurring late manifestations is meningovascular syphilis, in which the characteristic obliterative endarteritis involves the intracranial vasculature, causing strokes. Although the resultant clinical phenomena are described as protean, they are no more protean than in other cerebrovascular disease—differences reflect the site of damage, not the mechanism.

Several other characteristic abnormalities may occur. Those not due to vasculitis are collectively referred to as parenchymal neurosyphilis. Involvement of the upper brainstem and surrounding basilar cisterns may lead to Argyll Robertson pupils, small irregular pupils that do not react to light but do to accommodation. Optic atrophy may develop slowly, presumably owing to both increased intracranial pressure caused by the meningitis and local infiltration of the optic nerves. *Tabes dorsalis*, consisting of damage to the dorsal roots, the dorsal root ganglia, and the posterior columns, results in marked loss of proprioception, as well as "lightning-like" shooting radicular pain. Gait is typical of that in individuals with proprioceptive loss—slapping, with poor awareness of the location of the feet in space. Loss of the dorsal root ganglion neurons and dorsal roots leads to loss of reflexes and diminished pain awareness, potentially leading to repeated injuries to lower extremity joints with severe cumulative damage (Charcot joints).

One of the most fascinating disorders associated with late neurosyphilis is the late dementia, referred to as *general paresis of the insane*, or GPI. Initial symptoms are described as personality changes with delusions and hallucinations; seizures and myoclonus may occur. Involvement tends to be frontotemporoparietal, with a slowly progressive dementia. Considered a consequence of long-standing meningitis, the pathology is rather subtle. Inflammatory changes are seen in the ventricular walls (granular ependymitis). There is brain atrophy, ventricular enlargement, and neuronal loss, with some reactive gliosis. Parenchymal inflammation is usually rather limited, without evidence of multiple infarcts—in brief, the degree of CNS dysfunction seems out of proportion to the evidence of disease activity. MRI studies have demonstrated fairly widespread abnormalities.

Since the early 1980s, the HIV epidemic has led to a resurgence of neurosyphilis, raising new concerns about both the biology of the infection and its treatment. In HIV-infected individuals, early disease and asymptomatic disease each account for about one-third of the cases of co-existing neurosyphilis. Of patients with early disease, one-half have meningitis and one-fourth have meningovascular syphilis. Of those with late-stage disease, the majority has general paresis, and a small subset has tabes.

Finally, congenital infection still occurs. This happens most commonly during early stages of maternal infection, when spirochete dissemination is still actively occurring. Treatment during the first 4 months of gestation usually protects the fetus; after that, death of the fetus or newborn, or congenital infection, can result. The common manifestations of newborn infections include “snuffles” (rhinitis due to mucocutaneous involvement) and a diffuse rash that is unusual in that it involves the palms and soles as well as skin at mucoepithelial junctions. Involvement of the liver is common, as are osteochondritis and perichondritis, most typically manifested as a “saddle nose” and “saber shins.” Unusual, centrally notched, peg-shaped upper teeth (“Hutchinson’s incisors”) occur, as does frontal bossing. IgM assays can be useful for diagnosis.

Treatment

Treatment of early syphilis remains remarkably effective with simple regimens.[7] Primary, secondary, and latent syphilis (without CNS involvement and of less than 1-year duration) are generally treated with a single dose of intramuscular benzathine penicillin (2.4 million units). Treatment for 2 weeks with oral doxycycline (100 mg twice daily) has been recommended for patients allergic to penicillin, although few studies have evaluated this approach. Recommendations are usually for desensitization to penicillin if at all possible. When the nervous system is involved, high doses of intravenous penicillin are generally required (10 to 14 days, 3 to 4 million units every 4 hours). Curiously, for many years, weekly intramuscular injections of benzathine penicillin were used. This is still one of the recommended alternative regimens for neurosyphilis, even though the demonstrable levels in the CNS are subtherapeutic for *T. pallidum*, presumably reflecting the efficacy of this regimen outside the blood−brain barrier and the rather low incidence of late neurosyphilis in untreated individuals. An acceptable alternative is procaine penicillin 2.4 million units intramuscularly daily, with probenecid 500 mg orally four times daily for 10 to 14 days. Ceftriaxone has been suggested as an alternative in patients allergic to penicillin and may be useful.[8]

Treatment has been particularly challenging in patients coinfected with HIV. Not only may syphilis cause considerably more serious symptoms, it may be much more difficult to eradicate. Patients who have received full courses of usually curative doses of intravenous penicillin have developed clear-cut relapses, even when initial treatment was at a time when the patient was not severely immunocompromised.[9] This suggests that treatment may not eliminate these spirochetes entirely, but reduces the bacterial burden to a number that normally can be controlled by the patient’s immune system.

LYME DISEASE

Background

The term *Lyme disease* was coined in the mid-1970s to describe a disorder affecting children living near Lyme, Connecticut, who developed what appeared to be juvenile rheumatoid arthritis. Careful epidemiologic studies demonstrated that this disorder developed following bites by hard-shelled *Ixodes* ticks (Fig. 39-1), particularly when the bites were followed by a slowly enlarging erythroderm (Fig. 39-2), as reviewed in detail elsewhere.[6] It was soon recognized that this rash was identical to the one described early in the twentieth century in the European literature, known as

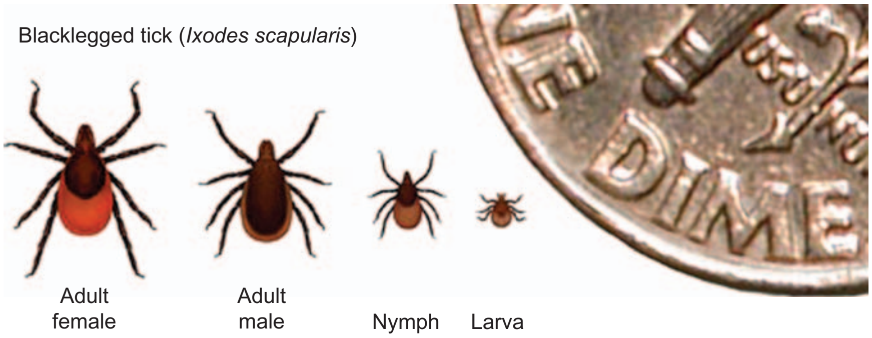

FIGURE 39-1 ■ Ixodes ticks. (Reproduced courtesy of Centers for Disease Control and Prevention: http://www.cdc.gov/lyme/transmission/. Accessed February 26, 2013.)

erythema chronicum migrans (ECM, now EM), also known to develop following bites of *Ixodes* ticks. Similarly, by the late 1970s it became apparent that affected individuals frequently developed all or part of a neurologic triad of lymphocytic meningitis, cranial neuritis, and painful radiculoneuritis, virtually identical to the disorder described in the 1920s by two French physicians and now known as Garin–Bujadoux–Bannwarth syndrome. A German report in 1941 even associated the disorder with "rheumatism." Although American patients appear to have more prominent rheumatologic symptoms and European patients more striking nervous system abnormalities, the European and American disorders are qualitatively similar.

In 1982, Willy Burgdorfer isolated a novel spirochete from *Ixodes* ticks collected on Shelter Island, New York (directly across Long Island Sound from Connecticut), and the following year it was clearly established that this organism, named *B. burgdorferi*, was the agent responsible for Lyme disease. Shortly thereafter, Eva Asbrink in Sweden identified a virtually identical organism as the agent responsible for European borreliosis. Subsequent studies have permitted the subdivision of this group of *Borrelia* (referred to collectively as *B. burgdorferi* sensu lato) into at least three subspecies. The strain responsible for North American disease has been termed *B. burgdorferi* sensu stricto, whereas European disease is attributed primarily to two strains, known as *Borrelia garinii*, responsible for most cases of neuroborreliosis, and *Borrelia afzelii*, responsible for several unique cutaneous abnormalities. These strain differences are believed to be responsible for the somewhat different range of presentations seen in Europe and North America. Several additional strains, *Borrelia mayonii* and *Borrelia miyamotoi*, have been identified in recent years, the former causing a Lyme disease-like illness, the latter one resembling relapsing fevers. Since both are quite uncommon and lack frequent nervous system involvement, they will not be discussed further here.

Interestingly, although Lyme arthritis was characterized only in the 1970s, identical cases of recurrent, nontraumatic knee arthritis were recognized years earlier in eastern Long Island, where this was known as Montauk knee. Some have conjectured that Lyme disease was introduced to the United States when a herd of deer was brought to Long Island, New York, from Europe early in the twentieth century, an interesting counterpoint to the theory that Columbus imported syphilis to Europe from the New World. The disease appears to have spread slowly from Long Island to Connecticut, and then to contiguous regions, and is now endemic along much of the eastern seaboard of the United States from Massachusetts to Delaware. A second endemic

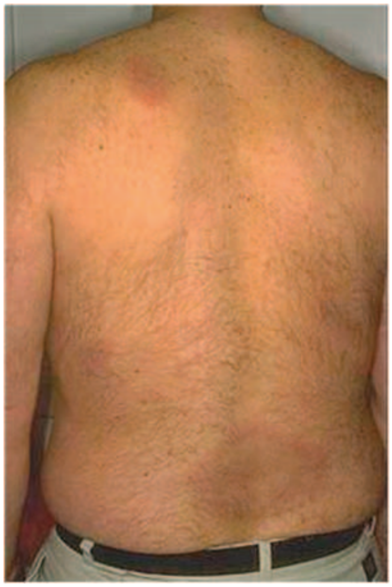

FIGURE 39-2 ■ Multifocal erythema migrans, extending across much of the back.

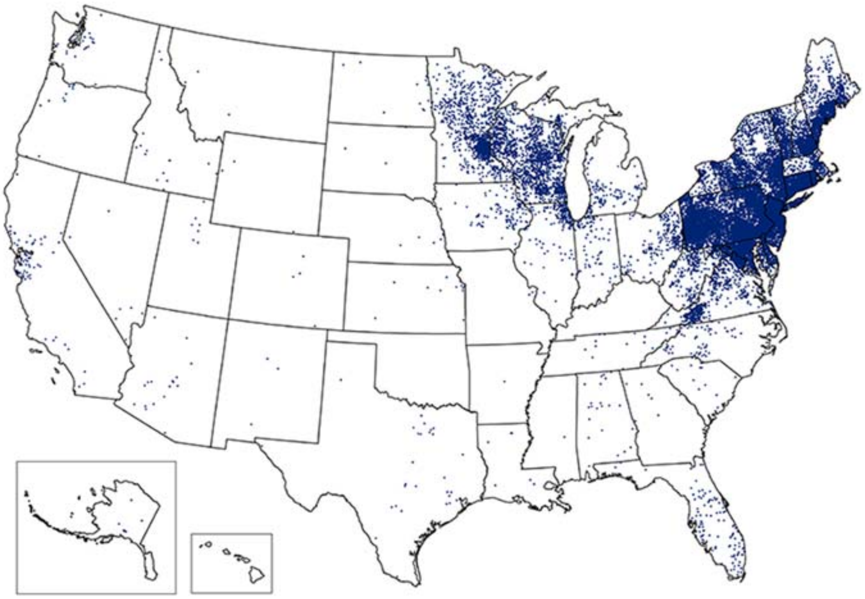

FIGURE 39-3 ■ Reported cases of Lyme disease in the United States, 2017. One dot is placed randomly within the county of residence for each confirmed case. Though Lyme disease cases have been reported in nearly every state, cases are reported based on the county of residence, not necessarily the county of infection. (Reproduced courtesy of the Centers for Disease Control and Prevention: Reported cases of Lyme disease—2017. https://www.cdc.gov/lyme/datasurveillance/maps-recent.html.)

focus exists in the upper Midwest, and possibly a small third one in northern California. These three regions account for the vast majority of cases of Lyme disease in the United States (Fig. 39-3).

B. burgdorferi spirochetes differ somewhat morphologically from *T. pallidum.* They range in length from 10 to 30 μm and are 0.2 to 0.5 μm in diameter. Like treponemes, they are helical in shape and propel themselves through medium or tissue with flagella.

Lyme disease occurs worldwide, primarily in areas in which *Ixodes* ticks co-exist with a reservoir of infected animal hosts and potential human victims. In temperate climates the tick goes through a 2-year life cycle. After hatching into a larva (Fig. 39-1), it feeds once, typically on a small mammal such as a field mouse. If this host has previously been infected, the tick may ingest spirochetes and itself become infected. After feeding, the larva matures into a nymph, which will then have its next meal. As blood enters the infected tick's gut, spirochetes already present proliferate. Over a period of 24 to 48 hours, they migrate to the tick's salivary glands, from which they can be injected into the new host, again transmitting infection. Because of this process, tick attachment lasting less than 24 to 48 hours is highly unlikely to result in infection.

The tick ultimately partakes of one last meal, this time as an adult. This typically occurs on a larger mammal, such as a deer, bear, or sheep—the species of choice giving rise to the popular name given the tick. Since the tick responsible for Lyme disease in the northeastern United States (*Ixodes scapularis*) is most closely associated with deer, some control strategies have focused on reducing the deer population. Although this may be helpful in lowering tick density, host elimination must be nearly complete. Similar strategies are less practical elsewhere. In much of the world, sheep provide the predominant large host. Elimination of these commercially important animals would be impractical. Other control strategies, such as providing rodents—the principal reservoir host—with acaricide-containing nesting material, springtime acaricide spraying to eliminate nymphs, and creation of dry barriers between wooded and residential areas, have met with varying success. In most endemic areas, ticks feed primarily during warmer months, placing human victims at greatest risk of contracting this infection from spring through autumn. The more temperate California climate leads to less seasonal variation.

Clinical Features

GENERAL

Lyme disease typically begins with a virtually pathognomonic rash, erythema migrans, occurring at the site of the tick bite, generally developing several days after but within 1 month of infection. Although the rash is erythematous and occasionally swollen, it typically is remarkably asymptomatic. Untreated, it expands to become many inches in diameter, potentially spanning an entire limb or occupying much of the trunk (Fig. 39-2). Between one-half and two-thirds of adults with Lyme disease recall having such a rash; in children, who are presumably under the watchful eye of a parent, the rash is seen in as many as 90 percent of infected individuals. Since the rash may occur on parts of the body not readily seen and is often asymptomatic, it is not surprising that a significant number of patients have no recollection of having had a rash. Like the chancre, it can resolve spontaneously without treatment, although treatment speeds resolution. Also like the chancre, the rash contains innumerable spirochetes, particularly at the leading edge. Unlike *T. pallidum*, however, it is possible to culture *B. burgdorferi* in vitro, although this requires a specialized medium that is not commonly available in most microbiology laboratories.

The spirochetes typically disseminate rapidly after inoculation. This secondary spread differentiates acute localized Lyme disease, analogous to primary syphilis, from early disseminated infection, analogous to secondary lues. Dissemination is often accompanied by fever and diffuse myalgias and arthralgias, identical to those seen in other bacteremias, often referred to as a "flu-like" syndrome. Notably, this flu-like syndrome does not include upper respiratory or gastrointestinal symptomatology. With dissemination, the rash may become multifocal (Fig. 39-2), and other organ systems may become involved.

Other cutaneous abnormalities occur infrequently in North America, but more commonly in Europe. Acrodermatitis atrophicans develops late in European borreliosis and consists of "tissue paper—like" atrophy of the skin, which becomes reddish-purple in hue. *Borrelia* lymphocytoma, a thickening of the skin due to a dense lymphocytic infiltrate, typically involving the earlobe or the areola of the breast, similarly occurs frequently in Europe but rarely in the United States.

In early series about 5 percent of patients (fewer in later studies) developed cardiac conduction abnormalities—commonly heart block in an otherwise healthy young adult. Occasional cases of myositis have been described. Mild elevations of serum creatine kinase are not uncommon, although frank muscle weakness is distinctly unusual. The myositis is typically focal, presents particularly with pain and swelling, and tends to occur adjacent to areas of skin, joint, or nerve involvement.

As in virtually every other known infection, a certain number of individuals become infected but do not become symptomatic, or develop minor symptoms that are self-limited and indistinguishable from other summertime febrile illnesses. The precise frequency with which this occurs is indeterminate, but probably is substantial.

Unlike syphilis, congenital infection does not appear to be a significant problem. Despite anecdotal reports, no characteristic "congenital Lyme disease syndrome" has been identified. Epidemiologic studies have failed to demonstrate any increase in adverse outcomes among women with positive serologies who have not had clinical evidence of acute infection. In a few instances, infants born to women who had experienced acute infections during pregnancy have themselves been infected, so aggressive treatment in this circumstance is appropriate.

NEUROBORRELIOSIS

Among infected patients, 10 to 15 percent will develop neurologic abnormalities, most commonly a lymphocytic meningitis, cranial neuropathy, or painful radiculitis. The neurologic syndromes can be categorized (Table 39-1) as affecting primarily the peripheral nervous system or the CNS, although overlap occurs. Manifestations of each vary widely, depending on the specific site and severity of involvement. However, all share just a small number of pathophysiologic mechanisms.

TABLE 39-1 ■ Central Nervous System Manifestations of Neuroborreliosis

Infection in Subarachnoid Space (Abnormal CSF)
Meningitis
Radiculitis
Cranial neuritis
Infection in CNS Parenchyma (Abnormal Neurologic Examination, MRI, CSF)
Encephalitis
Myelitis
Some cases of severe encephalopathy
Toxic or Metabolic Encephalopathy (Normal MRI, CSF)
Encephalopathy

CNS, Central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

The CNS is often seeded early in infection. Precise estimates are difficult because patients do not routinely undergo CSF examination. However, it is likely that the CNS is seeded in many individuals, but the infection clears spontaneously. In many patients, acute infection is marked by an acute lymphocytic meningitis. Headache and neck stiffness are quite variable in severity and do not correlate well with the degree of CSF pleocytosis. Typically, the CSF contains 50 to several hundred lymphocytes per cubic millimeter, with mild (50 to 150 mg/dL) elevations in CSF protein concentration. CSF glucose concentration is usually normal. Although culture of *B. burgdorferi* is technically possible, generally CSF cultures are positive in no more than 10 to 20 percent of patients with unequivocal Lyme meningitis—with only a minimal increase in detection rates using nucleic acid−based detection—probably reflecting the very low number of spirochetes free in the CSF.

Although this meningitis typically is benign and manifests primarily as a headache, particularly in children a disorder resembling pseudotumor cerebri may occur, with increased intracranial pressure. This generally occurs either with or following Lyme meningitis and presumably relates to impaired CSF resorption, to increased vascular permeability mediated by cytokines and therefore increased pressure, or to both. On rare occasions, this has resulted in significant visual impairment.

Actual infection of the brain or spinal cord parenchyma (encephalomyelitis) is extremely rare, probably affecting fewer than 1 in 1,000 infected, untreated individuals. In these rare individuals, there is generally clear clinical and MRI evidence of focal parenchymal involvement, usually affecting the white matter preferentially (perhaps reflecting preferential binding of *B. burgdorferi* to oligodendroglia). Patients may present with focal signs that depend on the site of involvement, although a myelopathy tends to be more common. Anecdotal case reports have described a remarkable range of neurologic presentations. Establishing a causal relationship in such circumstances can be challenging. A number of case reports, primarily of European patients, has suggested that, as in meningovascular syphilis, strokes may be caused by Lyme disease, but the evidence of a causal relationship is limited; if a meningovascular form of Lyme disease exists, it must be much less common than in neurosyphilis. Similarly, several reports have suggested that optic neuritis may occur in neuroborreliosis, but this association similarly is unclear.

Despite the potential severity of CNS involvement, antimicrobial therapy is usually highly effective. As with any disorder of the nervous system, established damage may leave residual deficits, but treatment in most cases will arrest any further worsening and usually results in demonstrable clinical improvement.

The final and most controversial syndrome has been a chronic encephalopathic state, referred to as Lyme encephalopathy. In rare, more severely affected patients, this may reflect a mild encephalitis. In the latter individuals, the CSF is virtually always abnormal and brain MRI may demonstrate focal abnormalities. In most, who have prominent non-neurologic involvement (most typically active, recurrent oligoarthritis), a mild encephalopathy occurs that is similar to that seen in patients with other chronic inflammatory disorders in whom there is a sense of chronic fatigue and malaise with blunting of intellect and memory. An important corollary of this is that it is difficult to attribute mental status changes to Lyme disease in the absence of either systemic or CNS inflammation.

Unfortunately, this concept has been expanded to describe a disorder referred to as “chronic Lyme disease.” Such patients probably fall into one of at least three groups. Rare patients with true CNS infection will fail to respond to standard courses of antimicrobial therapy. In these, a second course may well end the symptoms. Other individuals who clearly have Lyme disease and are microbiologically cured continue to manifest chronic and nonspecific symptoms. The etiology of these symptoms is unclear. However, these patients do not respond to additional antibiotics, but often respond to treatment directed at their symptoms with various combinations of exercise, “wellness education,” and medications including anti-inflammatory and antidepressant agents. In some, a sleep disorder is a prominent part of this syndrome and correcting this can be beneficial. Finally, this group has been shown to include numerous patients whose symptoms were never caused by Lyme disease in the first place. These individuals require careful evaluation to determine the actual cause of their symptoms, then appropriate treatment. It needs to be emphasized in this context that no systematic study has ever indicated that Lyme disease causes psychiatric disease, beyond the usual difficulties associated with being ill; in fact, a systematic study of more than 900 psychiatric patients in a Lyme disease-endemic area found no evidence of any associations between any specific psychiatric disorder and this infection.

The peripheral nervous system (Table 39-2) is probably involved more frequently than the CNS. The cranial nerves are at particular risk, probably because they are vulnerable both within the subarachnoid space and along their peripheral course. As in syphilis and other

TABLE 39-2 ■ Peripheral Nervous System Manifestations of Neuroborreliosis

Mononeuropathy Multiplex
- Radiculopathy
- Cranial neuropathy (particularly cranial nerves VII, VIII, III, V, VI)
- Diffuse polyneuropathy (confluent mononeuropathy multiplex)
- Brachial plexopathy
- Lumbosacral plexopathy
- Mononeuropathy multiplex
- Disorder resembling Guillain–Barré syndrome

Demyelinating Polyneuropathy (Anecdotal, Rare)

basilar meningitides, cranial nerves VII and VIII are frequently affected, although cranial nerves III through VI may also be involved. The lower cranial nerves are sometimes impaired, although much less frequently. Lyme disease is one of the few disorders commonly associated with bilateral facial palsies (along with sarcoidosis and Guillain–Barré syndrome). Because these cranial neuropathies generally occur fairly early in infection and because, in the most commonly involved areas, climate dictates that ticks feed primarily from spring through autumn, patients presenting with facial palsies in summer and autumn in endemic areas should undergo serologic screening for Lyme disease. CSF examination may be helpful to address alternative diagnoses. However, numerous European studies have shown that Lyme meningitis and cranial neuritis respond well to oral doxycycline, so the CSF findings will likely not affect treatment directly.

The syndrome of Garin–Bujadoux–Bannwarth is probably under-recognized in the United States. Patients typically have severe radicular pain that can precisely mimic the symptoms of a mechanical radiculopathy. Weakness in the same nerve root distribution ranges from minimal to severe. Truncal radiculopathies occur and, as with painful diabetic truncal neuropathies, may lead to considerable diagnostic confusion. A clue to this atypical etiology may be involvement of more than one dermatome. CSF is often, although not invariably, abnormal.

Some patients develop a plexopathy or a typical mononeuropathy multiplex. Patients with more longstanding infection may develop a milder, more diffuse polyneuropathy. This usually is not painful, but presents as a more mundane distal sensorimotor neuropathic syndrome, with both positive and negative symptoms. Interestingly, electrophysiologic and pathologic studies indicate that all these syndromes are due to a mononeuropathy multiplex. Notably, in the rhesus macaque monkey, the only animal model of human neurologic Lyme disease, virtually all infected animals develop a mononeuropathy multiplex that subsides over time.

Finally, rare patients have been described with a disorder resembling Guillain–Barré syndrome. Clinically, these individuals have had a rapidly progressive polyneuropathy, with ascending paralysis, but many have had a more prominent CSF pleocytosis than typically occurs in Guillain–Barré syndrome. Electrophysiologic changes have been varied but only rarely demonstrate prominent demyelination.

Diagnosis

Accurate diagnosis requires recognition of the clinical syndrome, a reasonable epidemiologic likelihood of exposure, and laboratory confirmation. Although much has been said in the past about the inaccuracy of testing for Lyme disease, it is comparable, overall, with other serologic testing. There remain technical arguments about the best antigen and methodology to use, but it is likely that more of the difficulty arises from misinterpretation of test results than from inaccurate ones.

Laboratory diagnosis relies primarily on serologic diagnosis—the demonstration of antibody in peripheral blood that adheres to *B. burgdorferi*. The sensitivity of microbiologic culture remains low (except in erythema migrans, where it is unnecessary) and probably reflects the small number of spirochetes present in readily accessible clinical specimens. The polymerase chain reaction assay has remained problematic, probably for the same reason (in addition to contamination-related issues leading to false-positive results). Antigen detection methods have not been found to be reproducible. Immune complexes containing *Borrelia* antigens have been described, but do not appear to be a reliable independent marker of infection. Hence, most laboratories rely on ELISAs to quantitate immunoreactivity.

Several particular problems confront serologic testing for Lyme disease. First, the disease is focally endemic. In highly endemic areas, such as areas of Long Island, 10 percent or more of the population may have been exposed. In contrast, in nearby New York City, there were about as many cases of malaria in 2010 as of confirmed Lyme disease. This highly varying background prevalence has a major effect on the positive and negative predictive values of test results, which depend on the background prevalence. In areas with Lyme disease prevalence of 1 in 100,000 and a statistically defined negative cut-off of 3 standard deviations, 1 sample in 1,000 will be a false positive, but only 1 in 100,000 will be a true positive. Second, as with any antibody-based testing, it must be remembered that it takes several weeks or more to develop a detectable antibody response in blood. Thus, negative results are common at the time of the erythema migrans, but, as with the syphilitic chancre, the rash by itself is sufficiently diagnostic to mandate immediate antibiotic treatment. Third, unlike other serologic tests, most clinicians rely on a single Lyme disease ELISA value rather than comparing acute and convalescent titers. This may be reasonable in syphilis, where screening reaginic tests are typically positive only during active infection, and is understandable insofar as there is a desire to treat Lyme infection as soon as possible. However, it makes test interpretation difficult in patients who have had prior infection and have a persistently elevated titer. As in most infections, the immune system usually continues to generate detectable antibodies for an extended period after the infection has resolved, sometimes making the relevance of the positive serology to current symptoms difficult to judge.

Finally, as with most serologic tests, some cross-reactions occur. To address this a two-step test procedure is used, but unfortunately this too has produced confusion. Western blots are routinely used to confirm positive or borderline ELISAs. The criteria for interpreting these (Table 39-3) were defined in individuals with positive or borderline ELISA results; therefore, they can only be applied in individuals with negative ELISA results with extreme caution. Second, the criteria were derived statistically. Interpretation is based not on the uniqueness of any of the bands but on the statistical probability of accurate diagnosis. Importantly, just as in syphilis, testing algorithms are evolving. While the standard approach for over two decades has been to screen with an ELISA and confirm positive or borderline results with the more specific Western blot, the CDC now also endorses an alternative approach, testing with two independent ELISAs (i.e., testing for reactivity to different antigens, much like the European algorithm for syphilis testing) provides better test accuracy and eliminates much of the confusion associated with Western blot interpretation.[10]

TABLE 39-3 ■ Western Blot Criteria for Confirmation of Positive Serology in Lyme Disease

IgM (2 required)	Bands (kDa)	23, 39, 41
IgG (5 required)	Bands (kDa)	18, 23, 28, 30, 39, 41, 45, 58, 66, 93

As in syphilis, spinal fluid studies can be extremely useful, but they also are the source of considerable confusion. Most, if not all, patients with active CNS infection will have elevations in the CSF white blood cell count, protein concentration, or both. Chronic infection is often accompanied by increased local production of antibodies, resulting in an increased relative CSF IgG concentration and even oligoclonal bands. In most acute cases (about 90%) and in many patients with more longstanding CNS Lyme disease (at least 50% and possibly more), synthesis of specific anti–*B. burgdorferi* antibodies in the CNS can be demonstrated by appropriately comparing concentrations of specific antibody in CSF and serum. Simple measurement of antibody concentration in the CSF alone can be very misleading in individuals with blood–brain barrier breakdown, CNS inflammation from other causes, or positive peripheral blood Lyme disease serologies, as discussed previously in considering CSF serologies in syphilis. Mounting evidence suggests that measurement of the B cell–attracting cytokine, CXCL13, in CSF may be useful in clarifying the diagnosis.[11,12]

Treatment and Outcome

As with any infection, prevention is usually simpler than treatment. Infected ticks occur in relatively restricted locales, and avoidance is therefore a feasible strategy. Those who cannot or choose not to adopt this strategy can limit their risk by wearing light-colored clothing that covers as much of the body as possible, making it easier to spot the very small, responsible ticks. Because ticks must be attached and feeding for 24 to 48 hours before infection is likely, a careful tick check at the end of the day is highly effective. Attached ticks should be removed by placing a fine forceps between the tick and the skin, and gently pulling back. Efforts to suffocate ticks in petroleum products or burn them with a lit cigarette are counterproductive. Use of acaricides can help, but repeated exposures, particularly in children and with higher-concentration products, may lead to significant systemic absorption and may be neurotoxic. A vaccine was available but was withdrawn from the market, primarily because of poor sales.

Antimicrobial therapy is highly effective, regardless of disease duration and severity. Popular mythology about the organism hibernating invisibly, only to resurface years later, is an intriguing theoretical possibility, but from a practical perspective is irrelevant. Patients with the characteristic rash should be treated immediately with oral

TABLE 39-4 ■ Treatment Regimens

Medication and Route of Administration (Duration)	Adults	Children*
Parenteral (2–4 weeks)		
Ceftriaxone†	2 g daily	50–75 mg/kg daily
Cefotaxime	2 g every 8 h	150–200 mg/kg daily in 3–4 divided doses
Penicillin	20–24 million units daily	300,000 units/kg daily, divided every 4 h
Oral (3, possibly 4, weeks)		
Doxycycline‡	100 mg twice to four times daily	4 mg/kg daily in two divided doses
Amoxicillin§	500 mg three times daily	50 mg/kg daily in three divided doses
Cefuroxime axetil§	500 mg twice daily	30 mg/kg daily in two divided doses

Modified from Treatment of Lyme disease. Med Lett 42:37, 2000, with permission.

*Pediatric dosage should not exceed adult recommendation.

†Ceftriaxone should probably not be used late in pregnancy.

‡Although prior guidance recommended against use of any tetracyclines in children younger than age 8, recent pediatric guidelines have relaxed that recommendation. That notwithstanding, there is no evidence of "breakthrough" neuroinvasive disease in children treated for EM with amoxicillin or cefuroxime axetil.[13] Doxycycline should probably not be used in pregnant women.

§Limited data but probably effective.

medication (Table 39-4), regardless of the results of serologic testing. Those with more disseminated disease may well respond to oral regimens, and there are excellent data that Lyme arthritis and meningitis will usually respond well to oral regimens, particularly with doxycycline. Although US practitioners tend to be reluctant to use oral regimens when there is evidence of CNS involvement (particularly CSF abnormalities), such patients—if there is no parenchymal CNS involvement—can be treated effectively with oral doxycycline (Table 39-4). The optimal duration of treatment remains unclear. No randomized trial has demonstrated any advantage of prolonging parenteral treatment beyond 2 weeks. However, anecdotal evidence from all major centers treating patients indicates that occasionally this is insufficient. As a result, courses of 3 to 4 weeks are used not uncommonly and, under exceptional circumstances, repeated. Despite common practice at some centers, available data do not support longer courses or the use of more toxic antimicrobials. Multiple studies have addressed the role of longer courses of antimicrobial therapy in patients with continuing but nonspecific symptoms; no sustained benefit has been found over conventional treatment.[14,15]

Several studies from Lyme disease–endemic areas should be highly reassuring. Systematic case-control studies from Connecticut and Nantucket Island, Massachusetts, both areas highly endemic for Lyme disease, provide clear evidence that long-term outlooks of treated patients are excellent. Many patients who have been diagnosed as having Lyme disease and have undergone treatment appear to develop the same transient symptoms as do normal control subjects; however, they attribute them to Lyme disease and therefore find them more distressing. As also supported by several prospective studies from endemic areas in New York State,[16,17] by all objective measures, treated patients appear indistinguishable from healthy, uninfected individuals.

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CHAPTER

40

Tuberculosis of the Central Nervous System

JOHN M. LEONARD

MENINGITIS
- Pathogenesis
- Pathology
- Clinical Presentation
  - *Symptoms and Signs*
  - *Atypical Features*
  - *Tuberculous Meningitis and HIV Infection*
- Diagnosis
  - *Cerebrospinal Fluid Examination*
  - *Neuroradiologic Evaluation*
  - *Differential Diagnosis*

TUBERCULOMA

SPINAL TUBERCULOUS ARACHNOIDITIS

THERAPY
- Antituberculous Chemotherapy
  - *Recommended Regimen*
- Adjunctive Therapy
  - *Corticosteroids*
  - *Surgery*

PROGNOSIS AND OUTCOME

CONCLUDING COMMENTS

Tuberculosis in all its forms remains a challenging clinical problem and a public health issue of considerable magnitude. Each year there are an estimated 10 million new cases of active disease worldwide and 1.3 million deaths attributable to tuberculosis. In 2018, 9,029 new cases of active tuberculosis were reported in the United States, an incidence rate of 2.8 cases per 100,000 persons.[1] Pulmonary tuberculosis accounts for 70 percent of active cases, isolated extrapulmonary disease 20 percent, and combined extrapulmonary and pulmonary disease 10 percent.

Tuberculosis of the central nervous system (CNS) accounts for approximately 1 to 2 percent of reported patients with active infection and 8 percent of all forms of extrapulmonary tuberculosis in immunocompetent individuals. While pulmonary tuberculosis in the United States has declined gradually in recent decades, the number of reported cases of meningeal tuberculosis has changed little and the case fatality rate remains high despite the availability of effective antituberculous therapy. CNS tuberculosis may be considered as comprising three clinical syndromes: meningitis, intracranial tuberculoma, and spinal tuberculous arachnoiditis.[2,3] All three forms of CNS infection are encountered with near equal frequency in regions of the world where the incidence of tuberculosis is high. In Europe and North America, where the incidence is lower and extrapulmonary tuberculosis is seen primarily in adults with reactivation disease, the large majority of cases present with meningitis.

MENINGITIS

Pathogenesis

Current understanding of the pathogenesis of CNS tuberculosis is based on a series of careful clinicopathologic correlations that date to the early part of the last century.[3] Conceptually, there is a two-phase process, beginning with the hematogenous dissemination of *Mycobacterium tuberculosis* (bacillemia) that follows primary pulmonary infection or late reactivation elsewhere in the body. During this hematogenous phase, small numbers of bacilli are scattered throughout the substance of the brain, meninges, and adjacent tissues, leading to the formation of multiple granulomatous foci of varying size and degree of encapsulation (tubercles). In

Aminoff's Neurology and General Medicine, Sixth Edition.
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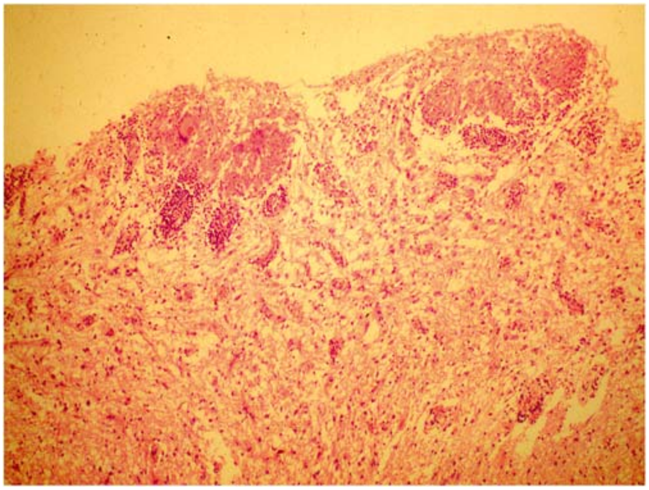

FIGURE 40-1 ■ Section from an autopsied case of tuberculous meningitis showing fresh granulomas beneath the surface of the brain, having eroded through the pia membrane into the subarachnoid space. (Hematoxylin and eosin, × 400.)

the second phase, such lesions coalesce to form larger caseous foci, some of which may lie just beneath the pia mater (the thin vascular membrane consisting of blood vessels and lymphatics that covers the entire surface of the brain) or beneath the ependyma (the thin nucleated epithelial membrane that lines the surface of the ventricles). With time and circumstance, a subpial or subependymal tuberculoma may destabilize and erode into the subarachnoid space, producing meningitis (Fig. 40-1). It follows that the propensity for developing clinical disease is determined by the number of tubercles and their proximity to the surface of the brain, the rapidity of progression, and the rate at which encapsulation follows acquired immunity.

The widespread and dense distribution of tubercles that occurs in progressive miliary tuberculosis greatly increases the chance that a juxtapial granuloma will be established and, from this critical location, break through into the subarachnoid space. This is the usual sequence in childhood tuberculous meningitis, as infants and young children are especially susceptible to progressive hematogenous dissemination following primary infection. Adult cases also develop in association with the bacillemia of progressive miliary disease or other less apparent or entirely hidden foci of chronic organ tuberculosis. Secondary hematogenous dissemination may be intermittent or chronic and progressive. In either circumstance, the spread of bacilli to distant organs produces scattered tubercles of varying size and encapsulation. Subpial tuberculous foci arising in this manner may remain quiescent for months or years, then destabilize when local injury or a depression in host immunity supervenes. Risk factors include advanced age, alcoholism, drug-induced immunosuppression, lymphoma, and infection with human immunodeficiency virus (HIV), all of which impair cellular immunity and, in persons with smoldering chronic organ tuberculosis, can lead to generalized tuberculosis including meningitis.

A significant proportion of adult cases of tuberculous meningitis have no demonstrable extracranial infection or apparent defect in host immune function. Occasionally, there is a history of head trauma some weeks or months prior to the onset of symptoms, suggesting that intracranial caseous foci may be destabilized by physical factors.

Pathology

The pathologic changes observed in the CNS result from an intense, cytokine-mediated hypersensitivity reaction induced by the presence of organisms and associated antigenic material in the substance of the brain and subarachnoid space. Three features dominate the pathologic process and account for the clinical manifestations: (1) a proliferative, predominantly basilar, arachnoiditis; (2) vasculitis of the arteries and veins traversing this exudate; and (3) disturbance of cerebrospinal fluid (CSF) circulation or resorption leading to hydrocephalus.

Proliferative arachnoiditis is most marked at the base of the brain and, in a matter of days or weeks, produces a thick, gelatinous exudate extending from the pons to the optic chiasm. With chronicity, the optochiasmic zone of arachnoiditis comes to resemble a fibrous mass encasing nearby cranial nerves and blood vessels.

Vasculitis with resultant thrombosis and hemorrhagic infarction develops in vessels that traverse the basilar or spinal exudate or those that are located within the brain substance itself. The vascular inflammatory reaction is initiated by direct invasion of the adventitia by mycobacteria or by secondary extension of adjacent arachnoiditis. An early polymorphonuclear reaction followed by infiltration of lymphocytes, plasma cells, and macrophages leads to progressive destruction of the adventitia, disruption of elastic fibers, and extension of the inflammatory process to the intima. Eventually, fibrinoid degeneration in small arteries and veins produces aneurysms, multiple thrombi, and focal hemorrhage in some combination. Depending on the location and extent of the vasculitis, a variety of stroke syndromes may result. Multiple lesions are common, and areas of ischemic injury that simulate lacunar infarctions most frequently involve the basal ganglia, cerebral cortex, pons, and cerebellum. Intracranial vasculitis and multiple infarcts are a common feature of autopsy studies and account for much of the residual neurologic disabilities observed in patients who survive.

Extension of the inflammatory process to the basilar cisterns impedes CSF circulation and resorption, leading to *communicating hydrocephalus* in most cases that have been symptomatic for longer than 2 to 3 weeks. Obstruction of the aqueduct develops less frequently from contraction of exudate surrounding the brainstem or from a strategically placed brainstem tuberculoma. In far-advanced cases, increased intracranial pressure may lead to brainstem compression and tentorial herniation.

TABLE 40-1 ■ Presenting Symptoms and Signs of Tuberculous Meningitis

Symptoms/Signs	Frequency (%)
Fever	60–90
Headache	40–90
Vomiting	30–60
Neck stiffness	40–80
Lethargy/drowsiness	25–80
Confusion	10–30
Stupor/coma	5–30
Focal neurologic signs	15–40
Cranial nerve palsy	20–40
Hemiparesis	10–20
Seizures	
Children	40–50
Adults	5

Clinical Presentation

SYMPTOMS AND SIGNS

Typically, tuberculous meningitis begins with a prodrome of insidious onset characterized by malaise, lassitude, personality change, intermittent headache, and low-grade fever. This is followed, usually within 2 to 3 weeks, by more prominent neurologic symptoms and signs such as meningismus, protracted headache, vomiting, confusion, cranial nerve palsies, and long-tract signs. The pace of illness may accelerate rapidly at this stage; confusion gives way to stupor and coma, seizures may occur, and multiple cranial nerve palsies and hemiparesis or hemiplegia are common. In most untreated cases, death supervenes within 5 to 8 weeks of the onset of illness although in occasional patients the illness follows a more indolent, slowly progressive course over weeks or months. In children, the condition is characterized early by irritability, loss of interest in play, restlessness, and anorexia; headache is less common and vomiting often much more prominent, especially in the very young. Seizures are more common in children and are likely to be an early or presenting symptom. Table 40-1 lists common symptoms and signs at presentation.

For purposes of prognosis and treatment, it is useful to categorize disease severity on presentation in reference to mental status and focal neurologic signs. *Stage I* comprises patients who have normal mental state, with or without meningismus but with no focal neurologic signs or evidence of hydrocephalus; *stage II* patients exhibit lethargy and confusion and may have mild focal neurologic signs such as single cranial nerve palsies and hemiparesis; *stage III* includes signs of advanced disease such as stupor and coma, seizures, multiple cranial nerve palsies, dense hemiplegia, and paraplegia. Some patients progress rapidly from one stage to the next within a few days of observation. The response to treatment is influenced significantly by the stage of disease at the time therapy is initiated, with better outcomes achieved when treatment is started early before the illness progresses from one clinical stage to the next.

ATYPICAL FEATURES

Adult patients may also present with a slowly progressive dementia over many months, characterized by personality change, social withdrawal, and memory deficits. At the other end of the spectrum are patients who present with an acute, rapidly progressive meningitic syndrome indistinguishable from pyogenic bacterial meningitis; at times, this accelerated form is superimposed on a chronic dementing illness. Seizures and focal neurologic disturbances such as cranial nerve palsies or hemiparesis may occur early and dominate the clinical presentation. Of the cranial nerves, the sixth is the most commonly involved, followed by the third and fourth. Occasionally the symptoms and signs of hydrocephalus with raised intracranial pressure (e.g., headache, papilledema, diplopia, and visual disturbance) precede signs of meningeal inflammation. Movement disorders, including tremor, myoclonus, chorea, and ballismus, may follow basal ganglia infarction secondary to vasculitis.

TUBERCULOUS MENINGITIS AND HIV INFECTION

CNS manifestations of tuberculosis are encountered with greater frequency in persons with tuberculosis who are coinfected with HIV. In a study of 455 HIV-positive patients with tuberculosis, 10 percent developed meningitis compared with 2 percent of HIV-negative patients, and HIV-positive patients accounted for 59 percent of all cases of tuberculous meningitis seen during the study period.[4] In comparison to non-HIV infected patients with tuberculous meningitis, coinfection with HIV has little impact on presenting clinical features, laboratory findings, or early response to therapy, though intracerebral tuberculomas are observed more commonly on neuroimaging studies in this population.

The initiation of antiretroviral therapy (ART) in treatment-naïve individuals coinfected with HIV and tuberculosis may lead to complications from the immune reconstitution inflammatory syndrome (IRIS) that follows restoration of immune responsiveness. Tuberculosis IRIS presents with signs of rapidly progressive extrapulmonary infection (e.g., fever, lymphadenopathy, respiratory symptoms, and meningitis) or clinical deterioration in patients previously improving on antituberculous therapy. In a series of 279 patients with tuberculosis-associated IRIS, progression to CNS tuberculosis developed in 12 percent, and excess mortality attributable to IRIS was observed in 30 percent of patients.[5] Manifestations of progressive CNS disease associated with IRIS include meningitis, brain abscess/tuberculoma, and rediculomyelitis.

Diagnosis

Few problems in medicine so critically challenge the physician's diagnostic acumen and clinical judgment as a patient with CNS tuberculosis. Once the possibility of tuberculous meningitis has been considered, the central task is rapid and thorough assessment of clinical and laboratory features followed by a prompt decision regarding empiric therapy.[6] Clues to the diagnosis include a positive family history of tuberculosis, recent exposure to others with active tuberculosis (especially in cases involving children and immunosuppressed adults), a history of recent head trauma, and alcoholism. Evidence of active tuberculosis elsewhere in the body, observed in 20 to 70 percent of cases, provides the most reliable basis for the presumptive diagnosis in patients with CNS disease. A meticulous physical examination should include looking for lymphadenopathy, spinal and other joint lesions, splenomegaly, scrotal masses, and draining fistulas. In patients with generalized (miliary) infection, careful funduscopic examination often shows choroidal tubercles on the retina: multiple, ill-defined, raised yellow-white nodules (granulomas) of varying size near the optic disc.

Abnormalities on chest radiography are seen in most childhood cases and in approximately 50 percent of adults presenting with CNS tuberculosis. Common findings include hilar adenopathy, a miliary interstitial pattern, apical scarring, or upper lobe nodular infiltrates. Computed tomography (CT) of the chest likely has a higher yield for these findings.

Patients with tuberculous meningitis may exhibit mild anemia and leukocytosis, but often the complete blood count and even the erythrocyte sedimentation rate are entirely normal. Hyponatremia related to inappropriate secretion of antidiuretic hormone occurs commonly and is a helpful, though nonspecific, clue to the diagnosis. The tuberculin skin test is more useful in childhood cases than in adults. A positive skin test supports the diagnosis but a negative skin test is relatively common in all forms of tuberculosis and thus does not exclude the diagnosis. Quantiferon gold serum testing is commonly used to assess for systemic infection but is neither sensitive nor specific for CNS disease.

CEREBROSPINAL FLUID EXAMINATION

Careful examination of the CSF is the key to diagnosis in most instances.[6] The opening pressure is usually elevated, the fluid is clear or "ground glass" in appearance, and, on standing, a delicate, web-like clot often forms. The typical CSF formula shows elevated protein and low glucose concentrations as well as a mononuclear pleocytosis.

The CSF protein concentration ranges from 100 to 500 mg/dL in most patients, is less than 100 mg/dL in 25 percent, and is more than 500 mg/dL in 10 percent. Patients with subarachnoid block may exhibit extremely high protein concentrations, in the range of 2 to 6 g/dL, associated with xanthochromia and a poor prognosis.

The CSF glucose concentration is usually low, being less than 45 mg/dL in approximately 80 percent of cases. The CSF cell count is between 100 and 500/mm^3 in most patients, less than 100 cells/mm^3 in approximately 15 percent, and between 500 and 1,500 cells/mm^3 in 20 percent. Although the characteristic cellular reaction is lymphocytic, early in the course of meningitis there may be only a few cells, a mixed pleocytosis, or polymorphonuclear predominance. This pattern will usually evolve in the direction of typical findings on repeat CSF examination. On occasion, an initial mononuclear pleocytosis may briefly change in the direction of polymorphonuclear predominance after therapy is initiated ("therapeutic paradox"), a change that may be associated with clinical deterioration.

Bacteriology

Specific diagnosis rests on the demonstration of *M. tuberculosis* in the CSF. Cultures are positive in approximately 70 percent of cases but often require weeks for detectable growth. Consequently, the careful examination of a stained smear for acid-fast bacilli (AFB) is the most effective means of making a prompt diagnosis. The importance of repeated, careful examination and culture of CSF specimens cannot be overemphasized; the diagnostic yield by smear and culture is enhanced when multiple CSF specimens from repeated lumbar punctures are submitted to the laboratory. In a prospective study designed to evaluate the effectiveness of careful bacteriologic technique, AFB were seen on smear in 77 of 132 adult patients (58%) and cultured from 94 of 132 (71%); the overall sensitivity of smear and culture was 82 percent.[7] This study confirmed earlier observations regarding the importance of high CSF volume and meticulous microscopy in the bacteriologic diagnosis of tuberculous meningitis.

In suspect cases, it is recommended that at least two CSF samples from separate lumbar punctures be obtained for stain and culture. It is best to submit 5 to 10 ml of the last portion removed; the AFB stain should be examined for 30 minutes. It is not necessary to defer treatment, as the yield remains high for several days after initiation of therapy.

Nucleic Acid Amplification Test

Molecular diagnostic techniques offer the promise of rapid and specific identification of mycobacteria in clinical specimens, thereby speeding the time to diagnosis and facilitating management decisions. Over the past decade, nucleic acid-based amplification (NAA) techniques have become increasingly utilized for the early diagnosis of tuberculous meningitis and for detection of drug resistance. In a recent meta-analysis of 63 studies comprising 1,300 patients with tuberculous meningitis confirmed by culture, the NAA test sensitivity and specificity were 82 and 99 percent, respectively.[8] CSF should be submitted for NAA testing whenever clinical suspicion is sufficiently high to warrant empiric therapy and initial stains for AFB are negative, recognizing that a negative NAA test result neither excludes the diagnosis nor obviates the need for continued treatment.

NEURORADIOLOGIC EVALUATION

CT and magnetic resonance imaging (MRI) have greatly enhanced the understanding of the pathogenesis, clinical assessment, and management of all forms of CNS tuberculosis.[9,10] CT can define the presence and extent of basilar arachnoiditis, the presence of cerebral edema and infarction, and the presence and course of hydrocephalus. In a study of 289 cases (214 children and 75 adults), hydrocephalus was demonstrated in 80 percent of patients, basilar meningeal enhancement in 39 percent, cerebral infarcts in 15 percent, and tuberculomas in 5 percent.[10] Hydrocephalus was associated with a longer duration of symptoms prior to treatment and was seen more often in children than adults. The CT findings are of prognostic significance and useful to monitor the effectiveness of adjunctive therapy such as corticosteroids and neurosurgical shunting procedures. In patients presenting with tuberculous meningitis, approximately 30 percent of those with stage I and 8 percent with stage II disease have a normal CT scan. Virtually all stage III patients have abnormalities, including hydrocephalus. Hydrocephalus alone without other features is uncommon and carries a good prognosis. Any degree of basilar meningeal enhancement combined with hydrocephalus is strongly suggestive of tuberculosis, and the combination is indicative of advanced disease, correlates well with the presence of vasculitis, and portends serious risk for basal ganglia infarction.[10]

MRI is the preferred imaging modality for defining lesions of the basal ganglia, midbrain, and brainstem.[9] It is superior to CT in delineating focal infarcts of the basal ganglia and diencephalon and in defining the presence of associated brainstem lesions. The character and severity of brainstem abnormalities correlate well with clinical signs of brainstem disease.

Differential Diagnosis

A variety of inflammatory, vascular, and neoplastic conditions of the CNS may mimic tuberculosis. In most cases, the differential diagnosis involves a patient presenting with clinical features of a granulomatous meningitis syndrome: fever, headache, meningeal signs, altered mentation, and a CSF profile showing lymphocytic pleocytosis, lowered glucose concentration, and high protein content. In addition to tuberculosis, the other primary infectious considerations include fungal disease (principally cryptococcosis), brucellosis, and syphilis. On occasion subacute aseptic meningitis with these CSF findings may be encountered in patients with unrecognized parameningeal suppurative infection such as sphenoid sinusitis, brain abscess, and endocarditis. Patients with herpes simplex virus and mumps meningoencephalitis may present with fever, rapid neurologic deterioration, and mild lowering of the CSF glucose concentration (see Chapter 42). Noninfectious etiologies to be considered include neurosarcoidosis and lymphomatous or carcinomatous meningitis. An evaluation for tuberculosis is warranted in every patient suspected of any of the diagnoses listed in Table 40-2.

TABLE 40-2 ■ Differential Diagnosis of Tuberculous Meningitis

Fungal meningitis (e.g., cryptococcosis, coccidioidal, histoplasmosis, blastomycosis)
Neurobrucellosis
Viral meningoencephalitis (e.g., herpes simplex virus, mumps)
Partially treated bacterial meningitis
Neurosyphilis
Focal parameningeal infection (e.g., sphenoiditis, brain abscess, endocarditis, spinal epidural abscess)
Central nervous system toxoplasmosis
Neoplastic meningitis (e.g., lymphoma, carcinoma)
Stroke
Neurosarcoidosis

TUBERCULOMA

Tuberculomas are conglomerate caseous foci within the substance of the brain that develop from deep-seated tubercles acquired during a recent or remote period of bacillemia. Centrally located, active lesions may reach considerable size without producing signs of meningeal inflammation. Under conditions of poor host resistance, this process may result in focal areas of cerebritis or frank abscess formation, but the more usual course is coalescence of caseous foci and fibrous encapsulation (tuberculoma). The characteristic CT finding is a nodular enhancing lesion with a central hypodense region.[9,11] Early-stage lesions may be isodense, often with edema out of proportion to the mass effect and with little encapsulation. As they mature, well-encapsulated tuberculomas appear as isodense or hyperdense lesions with peripheral ring enhancement. CT is useful for assessing the presence of cerebral edema, the risk of herniation, and the response to therapy. The MRI appearance depends on the stage of tuberculoma: focal cerebritis is manifest by nonspecific edema on T2-weighted images and ill-defined enhancement, whereas a caseating lesion typically shows central hypointensity and peripheral enhancement.

Clinically silent, single or multiple, small parenchymal tuberculomas are seen commonly in cases of tuberculous meningitis and often in miliary tuberculosis without meningitis. These lesions usually disappear with medical therapy, although cases have been reported in which tuberculomas enlarged early during the course of antituberculous therapy.

In contrast to small, incidental lesions that produce few or no symptoms, clinical tuberculomas presenting as symptomatic intracranial mass lesions are encountered frequently in areas of the world where the prevalence of tuberculosis is high. The usual patient is a child or young adult with headache, seizure, focal neurologic deficits, or signs of raised intracranial pressure. Symptoms of systemic illness and meningeal inflammation are usually lacking. The diagnosis is made with clinical, epidemiologic, and radiographic data or via needle biopsy.

Surgery for purposes other than diagnosis may be required when the location of the tuberculoma leads to obstructive hydrocephalus or compression of the brainstem. Corticosteroids aid in selected cases in which cerebral edema disproportionate to the mass effect contributes to altered mental state or focal neurologic deficits; however, this may mask the characteristic pathology of other diagnostic mimics such as CNS lymphoma, and therefore should be reserved for patients in whom the diagnosis is secure.

SPINAL TUBERCULOUS ARACHNOIDITIS

Tuberculous arachnoiditis or tuberculoma may arise at any level of the spinal cord in association with breakdown of a tubercle in the spinal cord or nearby meninges, or through extension from an adjacent area of inapparent spondylitis. The resultant inflammatory process gradually produces partial or complete encasement of the spinal cord in a gelatinous or fibrous exudate. In other cases, tuberculomas of the extradural, intradural, or intramedullary space may produce symptoms resembling local tumor.

Patients usually present with signs of nerve root and spinal cord compression secondary to impingement by the advancing arachnoiditis. The clinical manifestations are more neurologic than infectious, protean in nature, and often take the form of an ascending or transverse radiculomyelopathy of variable pace involving single or multiple levels.[12] Common symptoms and signs include pain, hyperesthesia or paresthesias in the distribution of the nerve root, lower motor neuron paralysis, and urinary or fecal incontinence. On occasion, the granulomatous mass or abscess may be confined largely to the epidural space, producing symptoms of spinal cord compression with no evidence of meningeal inflammation. Localized vasculitis can lead to thrombosis of spinal arteries and infarction of the spinal cord.

The diagnosis of spinal tuberculous arachnoiditis should be considered in the patient with any combination of the following clinical and laboratory features: subacute onset of spinal or nerve root pain; rapidly ascending transverse myelopathy or multiple-level myelopathy; increased CSF protein concentration and cell count; signs of arachnoiditis or epidural space infection by MRI; and evidence of tuberculosis elsewhere in the body. Surgical intervention and tissue biopsy are often required for diagnosis.

THERAPY

Antituberculous Chemotherapy

The decision to begin antituberculous chemotherapy should be made promptly and on the basis of strong clinical suspicion and presumptive diagnosis rather than waiting for confirmation of mycobacterial infection, as the prognosis is influenced greatly by the clinical stage at which treatment is initiated. There are no randomized trials to establish the optimal drug combination, dosage, and duration of treatment for tuberculous meningitis; the principles of treatment are those that govern the management of pulmonary tuberculosis. The use of multidrug regimens is designed to enhance the bactericidal effect, cover the possibility of drug resistance, and reduce the risk of emerging resistance while on therapy.

Isoniazid, rifampin, and pyrazinamide are each bactericidal, can be administered orally, penetrate inflamed meninges, and achieve CSF concentrations required for activity against sensitive strains. These drugs, in combination with ethambutol or streptomycin, are considered first-line therapy.

Isoniazid diffuses readily into CSF and achieves concentrations many times that required for bactericidal activity. The recommended daily dose is 10 mg/kg for children and 300 mg for adults. Pyridoxine, 25 or 50 mg daily, should be given concurrently to avoid the neurologic complications of isoniazid-induced pyridoxine deficiency, including peripheral neuropathy.

Rifampin is active early against rapidly dividing organisms and achieves reliable CSF concentrations only in the presence of meningeal inflammation. The daily dose in children and adults is 10 mg/kg (maximum 600 mg), and an intravenous formulation is available.

Studies of pulmonary tuberculosis have demonstrated that the addition of *pyrazinamide* to regimens that include isoniazid and rifampin produces a more powerful antituberculous effect without increasing the incidence of hepatotoxicity, as long as the duration of pyrazinamide therapy is restricted to 2 months or less. CSF penetration is excellent in the presence or absence of inflammation, and the drug is highly active against intracellular mycobacteria. It is recommended that pyrazinamide be included in the treatment regimen for meningitis during the first 2 months of therapy. In children, the daily dose is 15 to 20 mg/kg (maximum 2,000 mg). In adults, the dose is based on weight: 40 to 55 kg, 1,000 mg; 56 to 75 kg, 1,500 mg; 76 to 90 kg, 2,000 mg.

Ethambutol is a weak drug that reaches the subarachnoid space in moderate concentration. Its major toxicity, optic neuropathy, occurs in as many as 3 percent of patients receiving 25 mg/kg daily but is rare at the recommended dose of 15 mg/kg. When ethambutol is used, it is advisable to check baseline and then serial visual acuity, red-green color vision, and visual fields if possible.

RECOMMENDED REGIMEN

Clinical practice guidelines published jointly by subspecialty societies and the Centers for Disease Control and Prevention recommend an initial intensive phase of treatment with four drugs for 2 months followed by a prolonged continuation phase with two drugs for 7 to 10 months.[13] The initial four-drug regimen consists of isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin, administered for 2 months. This is followed by isoniazid and rifampin alone if the isolate is fully susceptible and the clinical course satisfactory. If pyrazinamide is omitted or not tolerated initially, the total duration of treatment should be extended to 18 months.

In managing ART-naïve HIV patients, the initiation of ART should be delayed until after 8 to 10 weeks of antituberculous therapy, regardless of CD4 count.[13] This is to avoid the enhanced risk of serious neurologic complications and excess mortality associated with IRIS in patients coinfected with CNS tuberculosis.

The possibility of drug-resistant tuberculosis should be anticipated in high-risk individuals such as those from areas of the world where tuberculosis is endemic, the homeless, patients who have received previous antituberculous drugs, and individuals with known exposure to persons harboring resistant organisms. The impact on therapeutic outcome is variable, depending on whether the isolate is resistant to isoniazid or rifampin or both. The best drug combination for resistant infection is uncertain and to some extent depends on the particular sensitivity pattern of a given isolate. Fluoroquinolones (levofloxacin and moxifloxacin) are bactericidal against mycobacteria and exhibit good CNS penetration. In regions where the incidence of isoniazid-resistant tuberculosis is high, or for any case where drug resistance is considered likely, it is advisable to intensify the initial regimen by increasing the dose of rifampin to 15 mg/kg per day and adding levofloxacin (or moxifloxacin) 20 mg/kg per day.[14] The duration of treatment for drug-resistant CNS tuberculosis should be extended to 18 to 24 months, taking into consideration severity of illness and clinical response.

Adjunctive Therapy

CORTICOSTEROIDS

The role of corticosteroids in the management of tuberculous meningitis has long been a matter of uncertainty. Older studies were limited by small numbers of patients and the failure to stratify severity of illness according to neurologic manifestations. There is however a growing body of clinical data demonstrating that adjunctive corticosteroid therapy reduces neurologic complications and improves survival in children and adults with CNS tuberculosis. A 2016 Cochrane systematic review and meta-analysis of published trials concluded that corticosteroids increase survival in non-HIV-infected patients with tuberculous meningitis, but is of uncertain benefit in individuals coinfected with HIV.[15]

Adjunctive corticosteroid therapy is recommended for patients with convincing clinical evidence of CNS tuberculosis.[13] Complications for which corticosteroids are thought to be most beneficial include increased intracranial pressure or cerebral edema, stupor, focal neurologic signs, and spinal block. Specific clinical indications based on urgent warning signs include the following: progression from one clinical stage to the next at or before the start of specific treatment, CT evidence of marked basilar enhancement, moderate or advancing hydrocephalus, spinal block or incipient block (CSF protein ≥ 500 mg/dL), and intracerebral tuberculoma when edema is out of proportion to mass effect with clinical signs.

There is no established protocol for corticosteroid administration in patients with CNS tuberculosis. A commonly used regimen for adolescents and adults is dexamethasone: 0.3 to 0.4 mg/kg per day for 2 weeks, then 0.2 mg/kg per day for 1 week, then 0.1 mg/kg per day for 1 week, then 4 mg/day orally while tapering 1 mg off the daily dose each week, total duration 8 weeks.

The decision to use corticosteroids should rest on a strong presumptive or positive diagnosis. Caution is advisable in the face of diagnostic uncertainty, especially for cases in which fungal CNS infection is considered a strong possibility. The expected benefit from corticosteroids must be weighed against the potential for adverse consequences, bearing in mind that initial improvement may be nonspecific for tuberculosis. In select cases, systemic antifungal therapy should be administered concurrently until an etiologic diagnosis has been reached.

SURGERY

The management of hydrocephalus may require surgical decompression of the ventricular system in order to prevent neurologic complications of sustained elevated intracranial pressure. The indications for surgery are failure to respond to medical management and noncommunicating hydrocephalus. In patients with communicating hydrocephalus at clinical stage II disease, serial lumbar punctures combined with corticosteroids, diuretics, and osmotic agents may suffice while awaiting the early response to chemotherapy. However, surgical consultation should not be delayed when these measures fail or when the clinical course is one of progressive neurologic impairment.

Surgical removal of intracranial tuberculoma may be necessary in the patient with clinical features of a single space-occupying lesion, midline shift, raised intracranial pressure, and lack of satisfactory response to chemotherapy and corticosteroids.

PROGNOSIS AND OUTCOME

The clinical outcome in any individual case is greatly influenced by age, duration of illness, clinical stage at the initiation of therapy, the extent and character of optochiasmic arachnoiditis, and vascular complications. In general, when antituberculous treatment is started before patients progress beyond stage I or during early stage II disease, cure rates of 85 to 90 percent may be achieved. Ages younger than 5 years and older than 50 years are associated with a poorer prognosis. The observed mortality rate exceeds 50 percent in patients older than 50 years, in persons coinfected with HIV, and in any patient with stupor and coma.

The incidence of residual neurologic deficits after recovery from tuberculous meningitis varies from 10 to 30 percent in recent series. Late sequelae include cranial nerve deficits, gait disturbance, hemiplegia, blindness, deafness, learning disability, dementia, and various syndromes of hypothalamic or pituitary dysfunction.

CONCLUDING COMMENTS

Tuberculosis of the CNS, principally meningitis, remains the most devastating form of active mycobacterial infection. The natural untreated history is that of insidious onset and subacute progression, prone to rapid deterioration once focal neurologic deficits occur, leading to stupor, coma, and death within 5 to 8 weeks of the onset of illness. Antituberculous chemotherapy is effective, and the best clinical outcomes are realized when treatment is started in the early stages of disease. Patients with a subacute meningitis syndrome and CSF findings of low glucose concentration, elevated protein level, and mononuclear pleocytosis should be treated promptly if there is evidence of tuberculosis elsewhere in the body or if initial evaluation fails to establish an alternative, more likely diagnosis. Serial sampling of the CSF for culture and stained smears combined with molecular diagnostic testing provides the best means for reaching a bacteriologic diagnosis. Treatment need not be delayed as culture and stain for AFB remain positive for some days after antituberculous therapy has been started. In the patient with compatible clinical features, CT or MRI evidence of basilar meningeal enhancement combined with any degree of hydrocephalus is strongly suggestive of tuberculous meningitis. Serial imaging is useful for following the course of therapy and for managing hydrocephalus. The treatment regimen for presumed drug-susceptible infection is isoniazid and rifampin in all patients, combined with pyrazinamide and ethambutol for the first 2 months. Adjunctive corticosteroids can ameliorate complications and reduce mortality. Surgical shunting should be considered early in the patient with advancing hydrocephalus and symptoms or signs attributable to raised intracranial pressure.

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CHAPTER

41

Leprosy

WINNIE W. OOI ■ JAYASHRI SRINIVASAN

INTRODUCTION
EPIDEMIOLOGY
HOST FACTORS
BACTERIAL FACTORS
CLINICAL MANIFESTATIONS
  Lepromatous Leprosy
  Tuberculoid Leprosy
  Borderline Leprosy
  Primary Neuritic Leprosy
  Autonomic Neuropathy in Leprosy
  Pain in Leprosy
DIAGNOSTIC STUDIES
  Electrodiagnostic Studies
  Ultrasonography
  Nerve Biopsy and Pathology
MYCOBACTERIAL TREATMENT
  Side Effects of Multidrug Treatment
  Drug Resistance and Treatment of Relapses
LEPROSY REACTIONS
  Type 1 Lepra Reactions (Reversal Reactions)
  Type 2 Reactions
LEPROSY AND HUMAN IMMUNODEFICIENCY VIRUS INFECTION
PREVENTION
CONCLUDING COMMENTS

INTRODUCTION

Leprosy is one of the oldest diseases known to afflict humans, with descriptions of the disease present in sixth century BCE Indian texts. It is caused by *Mycobacterium leprae* (*M. leprae*), the organism first identified by the Norwegian physician, Gerhard Hansen, in 1873. It is an obligate intracellular acid-fast bacillus, which is detected in tissues by the modified Fite-Faraco stain (Fig. 41-1). In 2008 a new species, *M. lepromatosis*, was identified in Mexico and is now known to cause a syndrome that is clinically equivalent in all respects to classic leprosy. Neither species grows in culture, and with the exception of armadillos, certain primates such as the chimpanzee and macaque, and red squirrels, humans are the primary reservoir and source of infection. The genome of the organism was sequenced in 2001 and has undergone reductive evolution, with only 49.5 percent of its genes being involved in coding.[1] The route of transmission is primarily through nasal droplets. Skin-to-skin contact is not thought to be an important route of infection. Other modes of transmission have been documented and are rare; they include contact with infected soil and direct dermal implantation such as occurs during tattooing. In susceptible individuals, the organisms rapidly gain access to cooler dermal tissues, primarily to cutaneous and subcutaneous nerves, and neural networks, skin appendages, sweat glands, and erector pili muscles. Scollard and colleagues demonstrated that endoneurial vessels in the armadillo serve as the route of entry into the nerve, by demonstrating extensive infection of endothelial cells of endoneurial, epineurial, and perineurial blood vessels.[2]

Leprosy is the leading cause of infectious neuropathy in the developing world. The considerable social stigma that has been associated with this diagnosis through the ages has persisted and can prevent early detection and effective treatment. Not only does *M. leprae* have a predilection for Schwann cells, but the immunologically mediated reactions seen during antimicrobial therapy cause significant damage to the peripheral nervous system and contribute substantially to disability.

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EPIDEMIOLOGY

The prevalence of leprosy, defined by the World Health Organization (WHO) as those who are on active mycobacterial treatment, has declined by 96 percent over the last 20 years. This is largely due to the worldwide implementation since 1982 of progressively shorter courses of multidrug therapy (MDT). By 1982, the incidence of leprosy had already declined significantly in countries such as China and Mexico, coinciding with improvement in nutrition and living conditions, and with widespread bacille Calmette-Guérin (BCG) vaccination, which is variably protective against leprosy.

Since the year 2000, however, some 200,000 new cases of leprosy have been detected every year. Although these new cases include individuals who acquired their infection years earlier, there is evidence that transmission of leprosy is continuing unabated, with delays in diagnosis and treatment. At least 9 percent of new cases over the past decade have been in children, and high rates of disability have been seen in new cases in several countries. The latest WHO target for 2020 includes decreasing the number of new patients diagnosed with deformities to less than one per million, and the number of children with disabilities to zero. The decreased incidence numbers do not take into account patients who have significant residual disabilities that require ongoing treatment or rehabilitation after completion of MDT. Furthermore, clinicians taking care of patients with leprosy will continue to treat relapses and reactions for years after completion of MDT.

HOST FACTORS

The clinical spectrum of leprosy correlates with the cell-mediated immunity of the patient. This is the basis for the Ridley-Jopling classification, which includes indeterminate leprosy (I), tuberculoid (TT), borderline tuberculoid (BT), borderline (BB), borderline lepromatous (BL), and lepromatous leprosy (LL) forms (Table 41-1). Patients with tuberculoid leprosy have an excellent cell-mediated immune (Th1) response to *M. leprae*. This manifests as few skin lesions, which histologically have well-organized granulomas (in which bacteria are rarely found) with CD4-predominant T cells. Patients who have less effective cell-mediated immunity have more aggressive clinical and bacteriologic expression of the disease, known as borderline disease. Finally, patients with LL are anergic to *M. leprae*, with predominant T-helper 2 (Th2) response, resulting in uncontrolled growth of bacilli and disseminated skin lesions. The reduced cell-mediated immunity to *M. leprae* in LL is specific for this organism and does not represent a generalized immune deficiency against other pathogens. Interferon-gamma (IFN-γ) production by T cells is another key component of the protective response against mycobacteria, as this

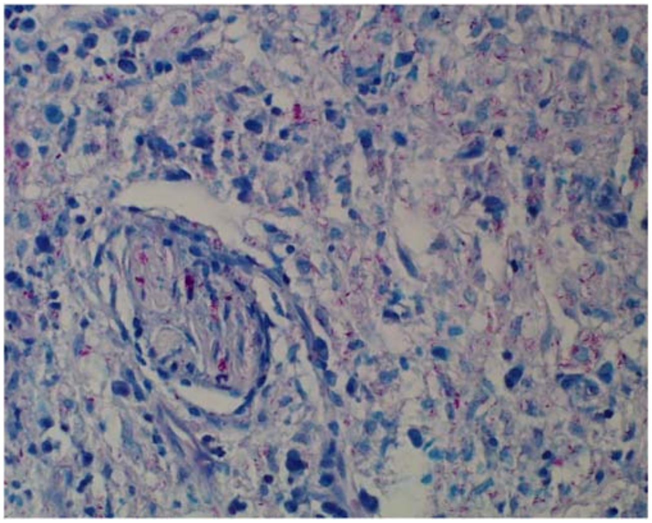

FIGURE 41-1 ■ Fite-Faraco stain reveals acid-fast bacilli in the nerve, seen in skin biopsy at 100× magnification.

TABLE 41-1 ■ **Spectrum of Leprosy**

Classification	*Leprosy Spectrum*				
Ridley and Jopling	**Tuberculoid**	**Borderline Tuberculoid**	**Borderline**	**Borderline Lepromatous**	**Lepromatous**
WHO	**Paucibacillary** Up to five skin lesions Slit skin smears negative		**Multibacillary** Six or more skin lesions (or any nerve involvement with few lesions) Slit skin smears positive		
	Higher	← Cell Mediated Immunity →			Lower

cytokine stimulates infected macrophages to kill intracellular *M. leprae*. In TT leprosy there is increased expression of type-1 cytokines IFN-γ and tissue necrosis factor-alpha (TNF-α), whereas in LL disease there is a predominance of the type-2 cytokines such as interleukin-10 (IL-10). Histologic examination of LL lesions reveals sheets of foamy macrophages in the dermis, containing large numbers of bacilli in microcolonies packed in parallel, like cigarettes in a packet, called "globi" with small numbers of $CD8^+$ T cells. In the WHO's simplified clinical classification scheme, TT and BT types are identified as "paucibacillary" (PB, 2 to 5 skin lesions) and types BB–LL as "multibacillary" (MB) (Table 41-1).

Genetic susceptibility to leprosy has been postulated as an important factor in the acquisition and manifestation of leprosy.[3] HLA genes may also influence the type of leprosy that develops; for example, tuberculoid leprosy develops more frequently in individuals with HLA-DR3, whereas LL is more prone to develop in those with HLA-DQ1 or HLA-MT1. Toll-like receptor (TLR) activation plays an important role in innate immunity to pathogens by the upregulation of antigen-presenting molecules and secretion of cytokines. Toll-like receptor 1 and 2 (TLR1 and TLR2) expression in monocytes has been found to correlate with the clinical presentation of leprosy, especially TLR2 microsatellite polymorphisms and TLR2 SNP. Patients with tuberculoid leprosy strongly express these receptors, whereas patients with LL express them weakly.

BACTERIAL FACTORS

M. leprae's affinity to Schwann cells is mediated by Fc receptors, complement receptors, the fibronectin binding protein, and TLR2.[4] Phenolic glycolipid 1 (PGL-1), which is an *M. leprae*-specific antigen, has been shown to bind to laminin of Schwann cells. PGL-1 also binds to complement (C3), and this complement–*M. leprae* complex in turn binds to macrophages and monocytes via complement receptors (CR1, CR3, and CR5), resulting in a three-component receptor–ligand–acceptor molecule for mediating phagocytosis of the organism by human monocytes. *M. leprae* attaches to Schwann cells via PGL-1, binding specifically to the G domain of the α-2 chain of laminin-2 (a protein constituent of the extracellular basal lamina) that, in turn, binds to α-dystroglycan on the plasma membrane of the Schwann cells.

In a classic series of experiments, Rambukkana and colleagues showed that *M. leprae* preferentially invades nonmyelin-producing Schwann cells where the organisms multiply in large numbers, serving as a reservoir for organism growth.[4] After attachment of the organism, myelin-producing Schwann cells undergo significant loss of myelination by an immune-independent mechanism. Dystroglycan complexes link the basal lamina to the cytoskeleton of Schwann cells through membrane-associated linker proteins called dystrophins or utrophins, which are believed to transduce signals from the exterior to the interior of the cells. Myelin-producing Schwann cells contain a third complex, dystrophin-related protein 2 (DRP2), the disruption of which results in demyelination of nerves. It is hypothesized that the loss of myelin production by infected Schwann cells in leprosy may be due to the interaction of PGL-1 with the DRP2–dystroglycan complex. This is followed by dedifferentiation of the Schwann cells to the nonmyelin-producing phenotype that is very vulnerable to invasion by the bacteria.

The survival of *M. leprae* within Schwann cells is greater at 33°C and therefore it has an affinity for nerves at superficial, cooler sites. The Schwann cells are also altered by infection, producing metabolic and functional changes that trigger the immune system in recruiting cytotoxic cells, T lymphocytes, and macrophages. The end result is unrestrained multiplication of the organism within Schwann cells, destruction of myelin, inflammatory changes, and secondary destruction of the nerve architecture. The discovery that demyelination can be induced in vivo by the bacterial cell-wall antigen alone may explain the ongoing neurologic damage that can occur in leprosy after treatment.

Nerve growth factor (NGF) is a neurotrophin produced by multiple cell types, including neurons, Schwann cells, lymphocytes, and mast cells. The role of NGF in leprosy is not fully understood but it is likely that it is involved in the nerve damage and ensuing neuropathic pain.[5] Studies have shown that higher levels of NGF are associated with LL and low levels are associated with tuberculoid forms of the disease. NGF may also play a role in neuropathic pain, and this may be an important pathway in developing future remedies for pain.

The genome of *M. leprae* is the smallest among mycobacteria, with approximately 1,605 genes encoding proteins and 1,300 pseudogenes. Compared to the bacterium causing tuberculosis, *M. leprae* reveals extreme reductive evolution with less than half of the genome containing functional genes. Reductive evolution, gene decay, and genome downsizing may explain the

TABLE 41-2 ■ Clinical and Histologic Aspects of Leprosy

	Tuberculoid Leprosy (TT)	Borderline Leprosy	Lepromatous Leprosy (LL)
Dermatologic features	Single or few anesthetic macules or plaques with well-defined borders.	Many anesthetic lesions with ill-defined to indistinct borders. Satellite lesions around larger lesions.	Multiple, nonanesthetic symmetrically distributed macules or papules progressing to diffuse infiltration of skin.
Clinical features of neuropathy	Asymmetric nerve enlargement usually found proximal to skin lesion.	Multiple nerves may be involved. Involvement is earlier and more rapid than in LL.	No neural lesions until late, when bilateral symmetric distal neuropathies occur.
Histopathology	Destruction of nerve architecture with granulomas in nerves. Bacilli rarely seen.	Findings range from those seen in TT to those in LL with variable presence of bacilli.	Greater preservation of nerve structure with sheets of foamy cells in the perineum resembling onion skins. Numerous bacilli are seen.

unusually long generation time and the inability to culture the organism in vitro. The genome is also highly conserved, with <300 single-nucleotide polymorphisms (SNPs) observed between distantly related strains, and only a few SNPs between closely related strains. Only 16 SNP subtypes have been defined. Genotyping *M. leprae* strains from around the world has enabled detailed phylogenetic and phylogeographic comparisons to be made, new mutations associated with antimicrobial resistance to be detected, and the likely origin of leprosy to be proposed. It has allowed the identification of the new species, *M. lepromatosis*, and the study of the presence of zoonotic leprosy in armadillos in the southern United States.

CLINICAL MANIFESTATIONS

The incubation period ranges from 3 months to 40 years, with an average of 7 years. The onset of the disease is insidious, with the skin and peripheral nervous system primarily being involved.[4] Three cardinal signs remain the mainstay for the diagnosis of leprosy in clinical practice: anesthetic skin lesions, enlarged peripheral nerves, and acid-fast bacilli demonstrated by Fite-Faraco staining in skin smears or skin biopsies (Fig. 41-1). The bacilli favor the cooler areas of the body, such as the chin, malar areas of the face, earlobes, buttocks, knees, and distal extremities. Skin lesions range from the asymptomatic, ill-defined, slightly hypopigmented, macule of indeterminate leprosy to the diffuse infiltration seen in LL that causes thickening of the skin of the face and earlobes (leonine facies). Approximately 5 percent of patients present with nerve involvement without skin lesions; this is called primary neuritic leprosy (PNL), the diagnosis of which may require nerve biopsy and polymerase chain reaction (PCR) assistance. The clinical and histopathologic features of the main types of leprosy are shown in Table 41-2.

Lepromatous Leprosy

The initial manifestations of leprosy are due to direct infection of dermal nerves resulting in anesthetic patches. The nerve damage extends from this early lesion with involvement of a small superficial nerve twig and skin anesthesia to infection of many nerves and involvement of larger skin areas. Patients may subsequently develop more widespread neuropathies with greater sensory and motor deficits, sometimes preceded by pruritus, paresthesias, and rarely pain. In untreated cases, this type of leprosy becomes widespread and symmetric within superficial skin tissues and peripheral nerves. Because the immune response to the bacilli in LL is very indolent, neuropathy usually evolves over many years. As in tuberculoid disease, neuropathies involving larger, superficially located nerve trunks in the face, arms, and legs may also occur.

Initially, there is loss of thermal sense followed by sequential loss of nociceptive and pressure sensations. The affinity of *M. leprae* for Schwann cells and their predilection for cooler parts of the body have made certain segments of nerve trunks vulnerable. The nerves most likely to be involved are the ulnar nerve at the elbow, the median nerve immediately proximal to the carpal tunnel, the radial nerve at the spiral groove, the peroneal nerve at the fibular head, the tibial nerve proximal to the ankle, and the facial nerve at the region of the zygomatic bone. Sensory nerves such as the superficial peroneal, posterior auricular, sural (Figs. 41-2 and 41-3),

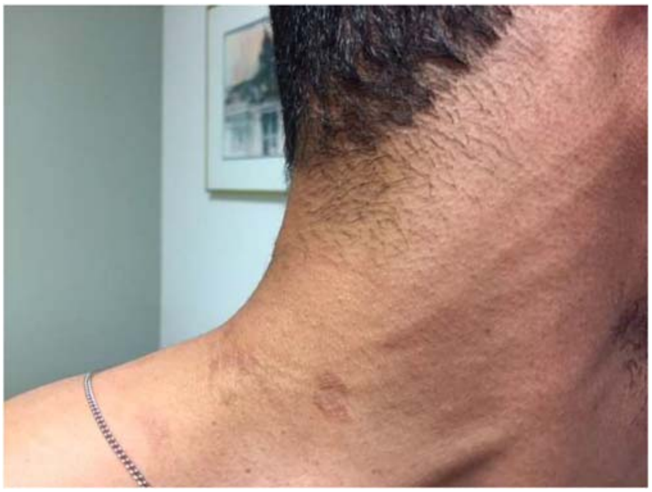

FIGURE 41-2 ■ Patient with tuberculoid leprosy and an enlarged posterior auricular nerve.

and superficial radial nerves and the dorsal branch of ulnar nerve may also be involved. Unperceived trauma secondary to sensory loss further aggravates the nerve damage.

Mycobacteria also invade the anterior chamber of the eye, upper respiratory tract, lymph nodes, periosteum, and testes. Eyebrows and eyelashes may be lost (madarosis), and anesthesia of affected areas is extensive and accompanied by anhidrosis. Sensory loss is largely due to destruction of intracutaneous nerve endings and first appears in cool areas, but with initial sparing of the soles of the feet and palms of the hands. There is also involvement of superficial facial nerve twigs, causing lagophthalmos and paralysis of some segments of the orbicularis oris and frontalis muscles. The sensory loss spares warmer areas including the intergluteal fold, the perineum, and the areas of the scalp covered by hair. Despite the appearance of an extensive sensorimotor neuropathy with clawed toes, foot drop, and clawed hands, preserved muscle stretch reflexes are the rule. Nerves that are grossly enlarged and infiltrated with abundant bacilli may still function well but are more susceptible to recurrent trauma.

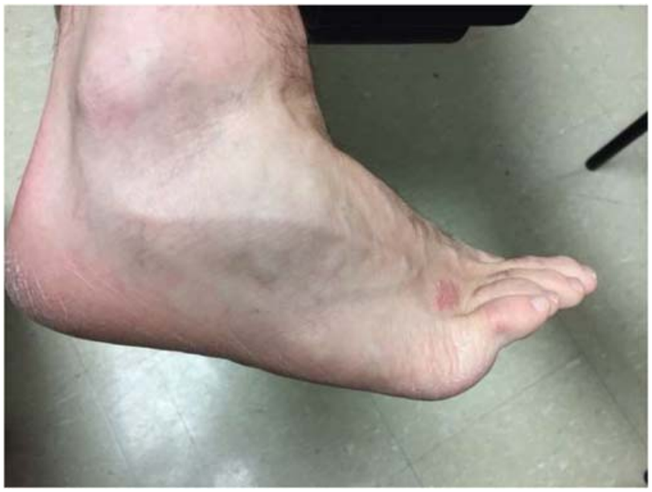

FIGURE 41-3 ■ Enlarged sural nerve with tuberculoid lesion.

Tuberculoid Leprosy

Nerve damage in tuberculoid leprosy is usually asymmetric and is often confined to the nerves underlying or near a skin lesion. Dermal nerves are infiltrated by granulomas composed of epithelioid cells and lymphocytes, with destruction of Schwann cells and secondary axonal damage. Nerves may be palpably enlarged and painful; calcification of nerves sometimes occurs in long-standing disease. The picture is generally one of a clearly visible skin lesion that is usually hypopigmented, with an elevated border (Fig. 41-3) and with a corresponding demarcated patch of sensory loss and absent sweating. Local bacillary invasion of nerves (although acid-fast bacilli are rarely seen on biopsy) and a robust immune response are the two factors that result in focal, limited, and asymmetric disease. Motor, sensory, or mixed nerves near a solitary tuberculoid patch may be affected. Subcutaneous sensory nerves near the tuberculoid patch are often enlarged. The tissue response within nerves may be so intense that there is necrosis and formation of a "cold" abscess. Enlarged nerves may be palpated or demonstrated on ultrasound.

Borderline Leprosy

Neuropathy in borderline leprosy can produce the most deformity as multiple nerves may be involved. Nerve damage occurs more rapidly than in LL and irreversible nerve destruction may occur. Borderline leprosy is immunologically unstable and movement along the spectrum may occur: either an upgrading response to the tuberculoid or a downgrading to lepromatous forms. When the clinical illness is toward the tuberculoid spectrum (BT), there may be a single lesion with asymmetric nerve involvement, but as the disease moves towards the lepromatous pole (BL) multiple symmetric skin and nerve lesions may be seen (Fig. 41-4).

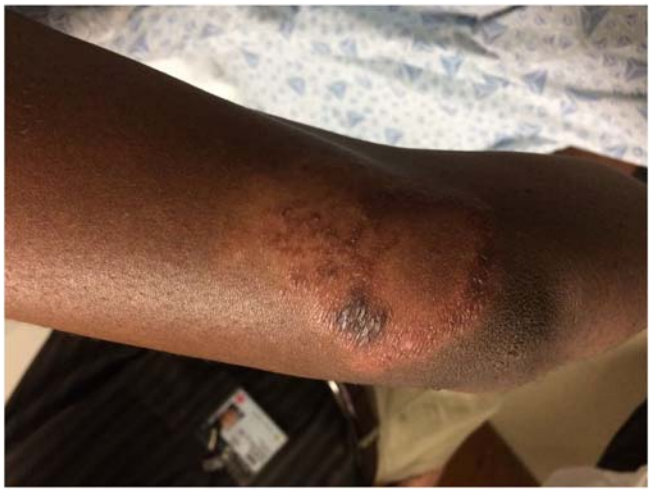

FIGURE 41-4 ■ Borderline lepromatous lesion.

Primary Neuritic Leprosy

This form is characterized by the presence of a neurologic deficit and nerve thickening (with or without tenderness) in the absence of clinical involvement of the skin or mucosa. This presentation is seen in 5 to 20 percent of patients at leprosy treatment centers in India. The clinical diagnosis of PNL may be difficult, as these patients do not have characteristic anesthetic skin lesions. However, blind biopsies of the skin near enlarged nerves often show the histologic changes of leprosy. Most of these patients present with a clinical picture consistent with mononeuritis multiplex, although in one-third a single nerve is affected. Nerve trunks may be significantly thickened and nodular. Ulnar and common peroneal nerves are commonly involved, although any nerve may be affected. Electrophysiologic studies reveal sensory and motor dysfunction of affected nerves, usually with demyelinating features early in the disease, and axonal injury in later stages. Nasal mucosal smears may show abnormalities including inflammation, epitheloid granulomas, and bacilli in half of the patients. Skin and nerve biopsies may show changes of leprosy (ranging from BT to LL), with bacilli in about 50 percent of patients. If nasal and skin pathology are nondiagnostic, nerve biopsies should be undertaken in patients suspected of having PNL. A positive PCR increases the sensitivity of detection of *M. leprae* in cases of probable PNL when Fite stain is negative.

Autonomic Neuropathy in Leprosy

Autonomic dysfunction occurs early in leprosy, especially in multibacillary disease, but it is often overlooked. Involvement of the small, unmyelinated, autonomic nerve fibers results in hypohidrosis and alopecia of the anesthetic, hypopigmented skin patches. Reduced sweating can often lead to dry, cracked skin that is prone to injury and infection. With more extensive skin involvement, there may be widespread impairment of sweating, resulting in heat intolerance. Impaired capillary blood flow due to involvement of autonomic fibers in blood vessels can result in stasis and impaired wound healing. Systemic symptoms from autonomic dysfunction may also be seen, including erectile dysfunction, heat intolerance, cardiac arrhythmias, and ankle edema. Testing will show vasomotor reflex impairment as measured by Doppler velocimetry, and absent sympathetic skin responses. Involvement of the parasympathetic system can be demonstrated by reduced heart rate variability on deep breathing and by the Valsalva maneuver. Autonomic dysfunction may impair the quality of life even after treatment, as patients may have persistent symptoms such as impaired sweating, heat intolerance, and severe xerosis.

Pain in Leprosy

Neuropathic pain is frequent in leprosy and may occur at all stages of the disease. Pain persists even after the patient has been fully treated. Studies have shown that the majority of patients have pain that is moderate to severe in intensity; this has a significant negative effect on their quality of life. Patients should be asked about their pain and treated for this with analgesic medications.

DIAGNOSTIC STUDIES

Electrodiagnostic Studies

Electrodiagnostic studies have contributed significantly to understanding the pathogenesis of the disease.[4] They also help in establishing a baseline against which response to treatment can be measured. Leprosy initially causes segmental demyelination of peripheral nerves with secondary axon loss. Early electrodiagnostic findings in the disease therefore include prolongation of distal latencies and segmental slowing of conduction velocities, particularly when measured across vulnerable sections of the nerves. If there is significant weakness on clinical examination, there may be evidence of conduction block or changes consistent with axonal loss, that is, a reduction in amplitude of compound muscle action potentials. Ulnar motor conduction studies reveal significant slowing of conduction across the elbow segment, with relative sparing of the forearm, wrist, and humeral segments. This selective involvement of the elbow segment reflects the predilection of the pathogen for cooler regions of the body. Median motor studies reveal slowing in the distal third of the forearm, usually proximal to the carpal tunnel. In the lower extremities, peroneal studies are usually abnormal, with slowing in conduction velocity in the segment between the popliteal fossa and the fibular head, and distally below the ankle, with prolongation of distal latency. Facial motor studies may also be abnormal, revealing prolonged latencies or reduced or absent responses of the orbicularis oculi or frontalis muscles. Even the phrenic nerve may be affected.

Needle electromyography may reveal reduced recruitment early in the disease, when there is weakness due to focal demyelination. Later, increased insertional activity and polyphasic, large-amplitude, long-duration motor unit potentials with reduced recruitment may be seen due to axonal loss and reinnervation. Late responses such as the F response and H reflex are often abnormal even without evidence of overt disease involving the nerves. Electrodiagnostic studies are sometimes used to monitor response to therapy or to monitor drug toxicity, particularly of thalidomide, which is known to be associated with neuropathy.

Ultrasonography

High-resolution ultrasonography is increasingly useful in leprosy.[6] This is a relatively inexpensive diagnostic method that is readily available, causes no discomfort, and can be used to obtain information that is static (size of the nerve, echo texture, nerve abscess) and dynamic (Doppler studies of neural blood supply). Studies have shown close correlation between abnormalities on ultrasound and nerve conduction studies in leprosy. While electrodiagnostic abnormalities may show evidence of nerve dysfunction, ultrasonography shows evidence of nerve enlargement, abnormal echo texture, and often increased epineural and endoneural blood flow. Additionally it sometimes pinpoints the site of maximum inflammation, which may help to determine the site of a nerve biopsy. In PNL, it may show nerve involvement that is more extensive than occurs in other mononeuropathies (such as entrapment neuropathies), nerve abscesses that are rare complications of PNL, and evidence of asymptomatic involvement of other nerves. A unique sonographic pattern of nerve enlargement is noted in patients with ulnar neuropathy; the enlargement starts at the ulnar sulcus and is maximal 4 cm above the medial epicondyle. Asymmetric increase of the cross-sectional area of the nerve at the same point between right and left sides is an important feature of leprosy. Finally, serial measurement of nerve thickness and echo texture as well as vascularity measurements by Doppler may help monitor response to treatment, and changes in these measurements may be early harbingers of relapse or the development of leprosy reactions.

Nerve Biopsy and Pathology

Nerve biopsies are rarely necessary in the right clinical and epidemiologic setting as the diagnosis is usually made clinically and confirmed by skin smears or skin biopsies.[2] However, nerve biopsies are sometimes necessary to confirm a diagnosis of leprosy, especially in PNL, or to exclude other causes of neuropathy. The nerve of choice is a sensory cutaneous nerve that is enlarged, such as the greater auricular (Fig. 41-2), superficial radial, dorsal ulnar, or sural nerve (Fig. 41-3). The histologic findings in nerve biopsies depend on the nature and severity of the leprosy as well as on the presence or absence of reactions.

In the tuberculoid (TT) and borderline (BT) subtypes, light microscopy of nerve biopsies may reveal a well-localized, intraneural granulomatous lesion involving a few nerve fascicles. Central caseous necrosis may be present, surrounded by inflammatory cells consisting of lymphocytes, epitheloid calls, and Langhans-type giant cells sometimes surrounded by regenerating myelin (Figs. 41-5 and 41-6). Bacilli are not seen commonly in TT or BT types and when present are usually

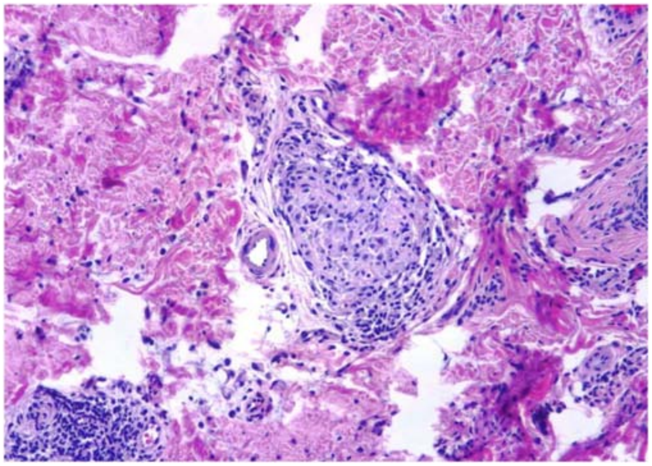

FIGURE 41-5 ■ Leprosy granuloma surrounded by lymphocytes.

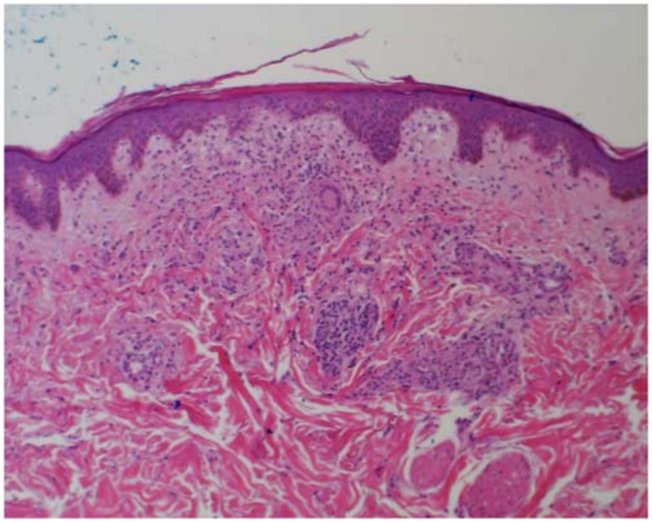

FIGURE 41-6 ■ Skin biopsy showing skin surface and non-caseating granulomas (with one multinucleate giant cell).

found in Schwann cells. Granulomas extend from the perineurium to the endoneurium and sometimes also involve the epineurium. Axon stains reveal significant axonal loss that is sometimes confined to certain fascicles of the nerves. In late stages, significant fibrosis and hyalinization of the endoneurium may occur and the nerve architecture may be destroyed completely.

In the BL and LL subtypes, there is usually greater histologic preservation of nerve structure than in the tuberculoid type; axon stains may reveal some axonal loss. Bacilli are numerous in Schwann cells and foamy macrophages (globi), and, to a lesser extent, in the endothelial cells of endoneurial and perineurial vessels. Plasma cells are characteristic of the lepromatous subtypes; histiocytes are seen in the early stages of infection while the presence of foamy macrophages indicates chronic infection. Epithelioid cells and nerve abscesses are usually not seen in the BL and LL subtypes (except when there is a change in the grade to a BT/TT subtype). The perineurium may be split into layers by edema or sheets of foamy cells, giving the appearance of an onion-skin. However, as the disease progresses, more significant destruction of the nerve architecture and matrix may occur; fibrosis may supervene with nerve destruction. Bacilli may be found in nerves for many years, even after treatment. Nerve biopsies may show active disease with intact organisms in some patients who are thought to have inactive disease clinically.

In borderline leprosy, nerve deformity may be significant. Multiple nerves may be involved as in lepromatous forms and there may be extensive nerve destruction as in tuberculoid leprosy.

PCR is very useful in diagnosing PNL when nerve biopsies have nonspecific changes and bacilli are not seen. PCR was positive in about 62 percent of all patients with PNL in an Indian study in which nerve biopsies were obtained in patients with mononeuritis multiplex. The positive and negative predictive values of PCR were 54.5 and 92.3 percent, respectively, in this population.[7]

MYCOBACTERIAL TREATMENT

In 1982, MDT was first recommended by the WHO to replace dapsone monotherapy to prevent the emergence of drug resistance.[5] The key component of these regimens was the bactericidal drug rifampicin. Since 1982 the recommended duration of treatment has decreased. The 2018 WHO guidelines (Table 41-3) recommend a three-drug regimen of rifampicin, dapsone, and clofazimine for all leprosy patients, to be given for 6 months for PB leprosy and 12 months for MB leprosy.

Patients with any nerve involvement (including primary neural leprosy) are treated as MB disease. This represents a change from the prior treatment for

TABLE 41-3 ■ **WHO Recommended Treatment Regimens**

			Duration	
Age Group	**Drug**	**Dosage and Frequency**	**MB (months)**	**PB (months)**
Adult	Rifampicin	600 mg once a month	12	6
	Clofazimine	300 mg once a month and 50 mg daily		
	Dapsone	100 mg daily		
Children (10–14 years)	Rifampicin	450 mg once a month	12	6
	Clofazimine	150 mg once a month, 50 mg on alternate days		
	Dapsone	50 mg daily		
Children <10 years or <40 kg	Rifampicin	10 mg/kg once a month	12	6
	Clofazimine	100 mg once a month, 50 mg twice weekly		
	Dapsone	2 mg/kg daily		

Note: The treatment for children with body weight below 40 kg requires single formulation medications since no MDT combination blister packs are available. For children between 20 and 40 kg, it would be possible to follow the instructions of the Operational Manual, Global Leprosy Strategy 2016–2020 on how to partly use (MB-Child) blister packs for treatment.
MB, multibacillary disease; PB, paucibacillary disease.

PB leprosy (which was rifampicin and dapsone for 6 months) due to evidence indicating better clinical outcomes with a three-drug, 6-month regimen. Published studies for patients treated with the prior two-drug PB regimen for 6 months showed that 2 to 44 percent of patients had clinically active skin lesions at the end of treatment. Nerve impairment occurred during treatment in 2.5 percent of patients, and visible disabilities increased from 4 percent at enrollment to 7 percent at 8 to 10 years of follow-up. Relapse rates ranged from 0 to 2.5 percent. For patients treated with the MB regimen for 24 months, one study in Thailand found that 29 percent of lesions were still active after 3 years and that visible disabilities increased from 5 percent at enrollment to 13 percent at 8 to 10 years of follow-up. Relapse rates were low, from 0.15 to 0.2 percent, but several reports have indicated much higher rates in subgroups of patients with high bacteriologic indexes (BI > 4 +), usually occurring 5 to 7 years after treatment is stopped. Relapsed patients responded to retreatment with the same drug combination, indicating that the relapse was not usually secondary to development of resistant organisms. Viable bacteria have also been demonstrated in patients who relapsed up to 13 years after MDT for MB disease.

A retrospective survey of 40 documented patients who relapsed showed that leprosy relapse after MDT usually occurred late and all had new skin lesions. Most relapsed with a positive skin smear after previously reaching negative BI status. The histologic features of relapsed BB-LL patients included granulomas containing macrophages or epithelioid cells, with sparse lymphocytes and acid-fast bacilli. PB patients require 2 years, and MB patients at least 5 to 10 years of monitoring after treatment. It may be difficult, however, to differentiate clinically between relapse, reactions, and recurrent infection. Immunologically mediated reactions occurring after completion of MDT are more frequent usually within the year after treatment completion. In addition, there may be persistent infection in nerves and eyes. DNA-based PCR-positivity and the presence of acid-fast bacilli by microscopic examination persist in some cases for years after treatment but do not necessarily reflect mycobacterial viability.

A promising new assay of *M. leprae* viability has been developed using 16S rRNA levels on skin biopsy specimens and may assist in differentiating between relapse and reactions after completion of MDT. Whole-genome sequencing techniques have also revealed that patients can be reinfected and did not relapse in recurrent leprosy cases. Many clinicians in resource-rich countries such as the United States have continued to use MDT for 24 months for MB disease until definitive data about relapses rates are available.

Side Effects of Multidrug Treatment

Although treatment with MDT is very effective, with over 95 percent cure rates, medications may occasionally cause serious adverse effects. The most common adverse effects reported are for dapsone, and include hemolytic anemia, methemoglobinemia, toxic hepatitis, photosensitivity, psychosis, and sulfone syndrome, currently described as DRESS syndrome (drug reaction with eosinophilia and systemic symptoms). Peripheral neuropathies have been observed among patients using dapsone in higher doses for dermatologic disorders. They develop painless distal motor axonal degeneration, most commonly involving the ulnar and median nerves. Usually only motor nerve involvement is seen, although sensory loss may also occur; this is usually reversible when dapsone is discontinued.

Clofazimine has rare serious adverse effects; the most common ones involve cutaneous hyperpigmentation (the most common cause of discontinuation of this drug), xerosis, ichthyosis, nausea, vomiting, diarrhea, and abdominal pain. In doses higher than 300 mg/day, clofazimine can be deposited in the intestinal wall, causing acute gastrointestinal obstruction. Rifampicin has been associated with toxic hepatitis, thrombocytopenia, flu-like syndrome, respiratory failure, hemolytic anemia, shock, and renal insufficiency.

Drug Resistance and Treatment of Relapses

The worldwide prevalence of drug resistance to *M. leprae* has not been established but reports from the WHO indicate a low level of resistance in some relapsed cases. Dapsone-resistant, rifampin-resistant, and multidrug-resistant (MDR) leprosy have been reported in different parts of the world, usually in association with relapse after insufficient therapy. Primary rifampicin resistance has also been reported, but clofazimine-resistant strains have not been demonstrated. PCR-based DNA sequence analysis of the *rpoB* gene of *M. leprae*, which is associated with rifampin resistance (Table 41-4), presents a cost-effective way for the study of drug resistance.

Dapsone resistance does not require a change of therapeutic regimen. If rifampicin resistance is proven, a WHO Expert Committee has recommended the regimen to follow (Table 41-5). Rifampicin resistance

TABLE 41-4 ■ Mutations in *Mycobacaterim leprae* Associated With Drug Resistance

Drug	Resistance Gene Mutation	Percent Resistant in Relapsed Cases
Dapsone	*folp* gene	5.9
Rifampicin	*rpoB* gene	4.1
Ofloxacin	*gyrA* gene	1.2

remains rare except in Brazil; therefore standard WHO-recommended MDT regimens remain the treatment of choice for relapsed leprosy everywhere. But primary multidrug resistance to rifampin and dapsone can also occur, as was described in a patient in the United States who originated in American Samoa.

Quinolone resistance in *M. leprae* is an increasing concern, especially in India; it may occur if ofloxacin is used for other acute infections. High dropout rates and a search for regimens with fewer side effects have led to trials with monthly rifampicin, ofloxacin, and minocycline (ROM). In a 2001 study, PB patients treated with either ROM or MDT for 6 months had similar cure rates of 97 percent. Both groups had similar relapse rates after follow-up for 5 to 8 years, but the rate of adverse effects was much lower in the patients receiving ROM.

Newer agents such as rifapentine (RPT) and moxifloxacin (MXFX), which are significantly more bactericidal than rifampicin, may represent other therapeutic alternatives. The bactericidal activity of a single dose of MXFX is identical to that of a single dose of rifampicin; both killed 92.1 percent of the viable *M. leprae*. The most promising new drug is bedaquiline, which is comparable to rifampicin in potency but has an entirely new mechanism of action and a long half-life. An international network of sentinel sites for drug-resistant leprosy was established in 2007 to share data and technical expertise, including trends in development of new drugs of relevance to leprosy.

TABLE 41-5 ■ Recommended Regimens for Drug-Resistant Leprosy

	Treatment	
Resistance Type	**First 6 Months (Daily)**	**Next 18 Months (Daily)**
Rifampicin resistance	Ofloxacin 400 mg* + minocycline 100 mg + clofazimine 50 mg	Ofloxacin 400 mg* OR minocycline 100 mg + clofazimine 50 mg
	Ofloxacin 400 mg* + clarithromycin 500 mg + clofazimine 50 mg	Ofloxacin 400 mg* + clofazimine 50 mg
Rifampicin and ofloxacin resistance	Clarithromycin 500 mg + minocycline 100 mg + clofazimine 50 mg	Clarithromycin 500 mg OR minocycline 100 mg + clofazimine 50 mg

*Ofloxacin 400 mg can be replaced by levofloxacin 500 mg OR moxifloxacin 400 mg.

LEPROSY REACTIONS

Leprosy reactions are immunologically mediated episodes of acute or subacute inflammation that may occur in any type of leprosy and result in increasing nerve damage and worsening disability. The two main types of reactions are type 1 and type 2 reactions (also known as erythema nodosum leprosum or ENL).[8] There is currently no cheap, accurate diagnostic test to detect reliably leprosy reactions or to predict which patients will develop these immunologic exacerbations, but various research strategies aimed at identifying biomarkers to diagnose these reactions are being pursued.

Type 1 Lepra Reactions (Reversal Reactions)

Type 1 reaction is seen almost exclusively in the borderline forms of leprosy (BT, BB, or BL) and is a manifestation of an improvement in the patient's immune response to the infection, commonly as a result of treatment. The incidence of reversal reactions is highest 6 to 12 months after initiating treatment but reactions may occur up to 5 years after diagnosis. They may be the presenting feature, especially during pregnancy or after the initiation of antiretroviral therapy (ART) in patients infected with human immunodeficiency virus. Clinical features of a type 1 reaction usually include an acute worsening of the swelling and erythema of preexisting skin lesions and development of acute, painful nerve palsies commonly involving the ulnar or peroneal nerve. Histologic features of a type 1 reaction are those of a delayed hypersensitivity response with $CD4^+$ lymphocytes, macrophages, and expression of IL-2 in the lesions. Intraneural caseous necrosis in tuberculoid disease and microabscesses in lepromatous disease can occur during reversal reactions. It is postulated that the lysis of mycobacteria by antibacterial treatment causes a release of antigen that mediates the immunologic response. *M. leprae* antigens and a diffuse extracellular infiltrate have been found in macrophages and

Schwann cells during reversal reactions, suggesting that these antigens are initiating factors in the reaction. Other studies indicate a strong Th1-like cytokine profile within reactional lesions. TNF-α, which has been shown to directly cause the destruction of myelin and oligodendrocytes in vitro, is also overproduced during reactions.

Corticosteroids are the treatment of choice for severe type 1 reactions, especially those involving ulcerations and neuritis.[9] Severe neuritis is treated promptly with prednisone at doses of 1 mg/kg daily, with increasing doses if there is no response within 24 to 48 hours. Corticosteroid therapy should be tapered slowly, especially in severe cases, to reduce the risk of relapse of the neuritis. Studies have indicated that moderate doses of corticosteroids given for 20 weeks are better than high-dose corticosteroids for 12 weeks in reducing the risk of relapse of neuritis. The approximately 60 percent success rate of corticosteroids in salvaging nerve function in reversal reactions is related to the promptness of initiation of therapy, as irreversible damage can ensue within hours to days. Corticosteroids have an immediate anti-inflammatory effect in reducing intraneural edema. More sustained benefit is probably due to its genomic effect, which affects cytokine production at various levels. The principal mechanism of action is thought to be inhibition of transcription of TNF-α—induced cytokine mRNA. A number of cytokine genes have the same TNF-α binding sites in their promoter regions, and corticosteroids downregulate the production of several proinflammatory cytokines, including TNF, IL-2, and IFN-γ.

Occasional patients with severe, protracted reactions require extended corticosteroid treatment for several additional months due to severe nerve pain. However, a Cochrane review of clinical trials has demonstrated that prolonged corticosteroid regimens of many months do not provide long-term functional neurologic benefits for most patients.[9] A more recent multinational randomized controlled trial comparing 45 to 60 mg methylprednisolone daily for 20 weeks versus 32 weeks for early ($<$6 months) nerve function involvement showed 78 percent improvement in both treatment arms. However, around 15 percent of the patients (comprising significantly more MB patients) in both groups required further individualized treatment because of reactions or deteriorating nerve function involvement, both of which occurred primarily in the first few weeks after corticosteroid treatment had ended. It appears that corticosteroids should be started as early as possible with acute neuritis but moderate doses should be continued for 20 weeks. Patients with higher BI should be monitored closely for recurrent reactions or deteriorating nerve function involvement for a few weeks after stopping, as they may need resumption of corticosteroid therapy.

Patients with pre-existing neuropathy have an increased risk of nerve function involvement and reversal reactions with treatment and this is not prevented by prednisone in the first 4 months of MB treatment. In contrast, a strong protective effect on neuritis was observed in those without significant loss of nerve function during the 4 months of prophylactic corticosteroid treatment and MDT, but this was not sustained at 1 year. Multiple or large lesions on the face overlying the distribution of the facial nerve may therefore benefit from low-dose prophylactic corticosteroids at the onset of MDT to prevent facial palsy, lagophthalmos, and ensuing exposure keratitis. Both cyclosporine and azathioprine have also been tried with varying success for their steroid-sparing effect. Corticosteroids have to be used in the first 5 days in patients treated with cyclosporine, until this drug reaches a steady state. Acute neuritis in reversal reactions that have not responded to high-dose corticosteroids for 6 weeks may be considered for surgical decompression (neurolysis) to relieve the pressure and preserve function, although there have been no large-scale controlled studies of this modality of treatment. Thalidomide has not been successful in the treatment of reversal reactions, perhaps because T-cell activation appears to be a significant component of reversal reactions and thalidomide stimulates T-cell activation.

Type 2 Reactions

ENL reactions occur almost exclusively in patients at the lepromatous end of the spectrum (BL and LL) and continue to be the most common cause of hospitalization. They usually occur within 2 years of the start of therapy, but rarely may be the presenting symptom. Risk factors for ENL reactions include antibacterial therapy, female sex, pregnancy, and high bacterial loads. Clinically, presentation is with crops of new painful erythematous papules that may resolve spontaneously. Other features include severe fatigue, fever, acute neuropathy, lymphadenopathy, uveitis, orchitis, mastitis, periostitis, and glomerulonephritis. Laboratory tests may reveal anemia, leukocytosis, and abnormal liver function tests. In contrast to type 1 reactions, patients tend to develop chronic recurring bouts of ENL reactions. In the MDT era, ENL occurs in 16 to 47 percent of LL patients and 2 to 11 percent of BL patients. ENL reactions are thought to be associated with the release of *M. leprae* antigens from dead and dying bacilli, inducing humoral immune mechanisms and immune complex formation, accompanied by high levels of circulating concentrations of TNF. These complexes result from an antigen–antibody reaction involving activation of the complement system and may resemble the Arthus phenomenon, resulting in systemic vasculitis and panniculitis.

The management of ENL is aimed at controlling the acute inflammation and neuritis, providing pain relief, saving vision, and preventing further attacks. Mild symptoms in the absence of neural and ophthalmologic symptoms may be treated with comfort measures and nonsteroidal anti-inflammatory drugs. Clofazimine at high doses up to 300 mg per day, with slow tapering over a year, can be effective for more severe cases of ENL without neural involvement. The drug of choice for treating the severe systemic symptoms associated with ENL is thalidomide. This drug accelerates the degradation of mRNA encoding TNF-α, resulting in its decreased production by monocytes and macrophages, without significantly reducing the production of other monocytic cytokines. Fever, fatigue, and skin lesions respond within a few days to thalidomide but neuritis accompanying ENL may take up to a week to respond.

Corticosteroids, with their more rapid effect in reducing intraneural edema, are often added to treat severe neuritis and prevent further nerve damage. High-dose pulse dexamethasone and azathioprine have been utilized in cases of recurrent ENL unresponsive to standard prednisone therapy. Successful treatment with methotrexate, in corticosteroid- and thalidomide-resistant ENL has also been reported. Methotrexate exerts anti-inflammatory and immune-suppressive effects.[10] It has direct inhibitory effects not only on the proliferation of cells involved in inflammatory reactions but also on proinflammatory cytokines. The immunomodulatory activity of thalidomide mainly lies in its capability to alter the secretion and activities of various cytokines including iL-6, IL-10, IL-1, and TNF-α; these cytokines are also targeted by methotrexate. The newer TNF-α blockers such as infliximab have been reported to precipitate the development of clinical symptoms in latent leprosy in some patients with rheumatoid arthritis. Chronic steroid-dependent ENL has also been found to be due to rifampin resistance and responded to an alternate regimen of minocycline, ofloxacin, and clofazimine.[11]

In addition to severe teratogenicity, which limits its use in women of child-bearing age, thalidomide may cause an axonal, length-dependent, sensorimotor neuropathy which presents with painful paresthesias or numbness. The incidence rate is maximal during the first year of treatment and is dose dependent.

In a study in which patients underwent neurologic examination and nerve conduction studies during treatment, thalidomide-induced neuropathy was seen in 25.2 percent of patients. The risk of neuropathy was highest when the daily dose exceeded 75 mg. No neuropathy was observed when daily doses of less than 25 mg were used. A recent review of the literature from 1965 to 2017 found thalidomide toxicity in less than 5 percent of patients.[12] Sural nerve biopsies have shown evidence of Wallerian degeneration and loss of myelinated fibers in thalidomide toxicity. Monitoring sensory nerve action potential amplitudes by nerve conduction studies may be useful for the early detection of thalidomide neuropathy, a decline in amplitude of 40 percent compared to the baseline usually being associated with clinical symptoms of neuropathy. Monitoring F waves may also be useful to detect early thalidomide neuropathy; F-wave chronodispersion may occur before changes in sensory amplitudes. Other adverse effects associated with thalidomide include deep venous thrombosis in 14 percent of patients.

LEPROSY AND HUMAN IMMUNODEFICIENCY VIRUS INFECTION

The interaction of leprosy and HIV coinfection is an evolving picture and has been significantly impacted by more widespread ART.[13] HIV affects cell-mediated immunity, and it was initially thought that the decrease in CD4 cells may result in an increase in disseminated leprosy. However, to date there are no clinical data to suggest that leprosy may worsen HIV infection or that HIV infection increases the risk of leprosy. All types of leprosy have been reported in HIV-infected patients, suggesting that HIV infection does not increase the rate of lepromatous disease. Coinfected patients treated with standard-length WHO-MDT regimens have responded adequately but in one study a 3.4 percent relapse rate occurred in coinfected patients compared to 1.0 percent in HIV-negative patients. This suggests that patients with coinfection should be monitored more closely for relapse after treatment. There are some data in coinfected patients that suggest that they may be at a higher risk of developing acute and recurrent reactions, especially when they are on ART.

In 1995, before widespread ART use, patients with AIDS and BT leprosy had lesions with well-formed granulomas and normal CD4 cell numbers in their lesions even though they had low circulating CD4 counts. Coinfected patients with LL had lesions with loose infiltrates comprising heavily parasitized macrophages and a small number of almost exclusively CD8 lymphocytes, which was similar to HIV-negative patients.

When a coinfected cohort treated with ART was followed prospectively, BT leprosy was the most common clinical form studied. Coinfected patients who present with BL leprosy and AIDS may shift to BT disease after implementation of ART and MDT, which suggests that, in some patients, granuloma formation might be altered by an ART-induced increase in the $CD4^+$ T-cell count. Histopathologic follow-up of these patients has revealed that on initiation of ART and MDT foamy histiocytes containing numerous acid-fast bacilli are replaced by granulomas consisting of lymphocytes and epithelioid cells with scant or no acid-fast bacilli. These findings demonstrate the true impact of HIV infection, ART, and MDT on leprosy granuloma formation. Immunostaining techniques revealed the absence of $CD4^+$ T cells in all granuloma specimens from the patients with BT disease, but $CD3^+$ T cells, macrophages, and natural killer cells were observed within the granulomas. These observations indicate that cell types other than $CD4^+$ and $CD8^+$ T lymphocytes may be playing a role in granuloma formation under the conditions observed for individuals with leprosy and HIV infection receiving ART. Further studies aiming to investigate this possibility are currently ongoing.

Another consequence of ART-induced $CD4^+$ T-cell count improvement is the development of immune reconstitution inflammatory syndrome (IRIS). IRIS is a paradoxical deterioration in clinical status after starting ART, a deterioration that is attributable to the recovery or reactivation of the immune response to a latent or subclinical process. This syndrome was first associated with leprosy in 2003 and usually develops within 6 to 10 months after initiating ART. Risk factors include advanced HIV disease with CD4 counts below 50 before ART. BT leprosy was the commonest form detected and type 1 (reversal) reaction was always present. Ulceration, a highly unusual feature in leprosy lesions, was commonly observed.

The neuropathies associated with HIV have been well described. A few small studies in the 1990s did not find increased nerve damage in coinfected patients. Subsequently it was found that leprosy patients coinfected with HIV (87% on ART) when compared to patients with leprosy alone had a greater rate of overall nerve function involvement, especially in MB disease. The most frequent onset of leprosy in relation to ART was within 12 months of the introduction of therapy. Nerve function involvement improved over time using MDT and ART. Neuritis was treated with prednisone at doses recommended by the WHO, and coinfected patients had the highest rate of clinical improvement in the first 60 days.

PREVENTION

Prevention of leprosy with vaccines directed against *M. leprae* or other mycobacterial antigens has thus far not proved to be too effective in large-scale clinical trials. BCG appears to be protective against leprosy in some populations but not in others. Repeated doses of BCG vaccine may be more effective, but this approach has limited clinical application, because of the cost of implementation and the potential for adverse reactions in immunosuppressed patients. Mapping of the *M. leprae* genome and the discovery of the armadillo as a good animal model for leprosy pathogenesis have led to better understanding of immunology with potential for identification of candidate antigens for vaccine development.

LepVax, a defined subunit vaccine that provides effective pre-exposure and postexposure prophylaxis of *M. leprae* infection, is in early clinical trials.[14] It appears safe and, unlike BCG, alleviates and delays the neurologic disruptions caused by *M. leprae* infection. MDT does not eliminate transmission in households, and early detection of subclinical leprosy or the carrier state is difficult. The identification by PCR (or other methods) of high-risk household contacts who may benefit from vaccination or chemoprophylaxis deserves further study. The 2018 WHO guidelines recommend the use of single-dose rifampicin as preventive treatment for adult and child (2 years of age and older) who are close contacts of leprosy patients, after excluding leprosy and TB disease.[15] This is based on the COLEP2 randomized controlled trial that found single-dose rifampicin in leprosy contacts led to a

57 percent reduction in the risk of leprosy after 2 years and 30 percent after 5 to 6 years.

CONCLUDING COMMENTS

The discovery that demyelination can be induced by dead *M. leprae* or its bacterial cell wall alone, both in vitro and in vivo, and the use of armadillos as animal models to study the pathogenesis of nerve damage have provided new insights into the underlying causes for continuing neurologic injuries in patients who have been bacteriologically cured of leprosy after MDT. Leprosy will continue to occur in endemic and nonendemic countries where physicians are becoming less familiar with the clinical presentation of a disease for which early diagnosis and MDT treatment are crucial to prevent new and ongoing nerve damage. Successful application of modern molecular methods using current knowledge of the bacterial genome and host susceptibility factors, should lead to better identification of target *M. leprae* antigens for improved diagnostic testing, vaccine development, identification of new antimicrobial agents, and detection of relapses after therapy. An improved understanding of nerve damage and reactions should lead to better preventive and therapeutic modalities.

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CHAPTER

42

Nervous System Complications of Systemic Viral Infections

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PATHOGENESIS OF VIRAL CENTRAL NERVOUS SYSTEM INFECTIONS
VIRAL MENINGITIS
  Enteroviruses
  Herpes Simplex Virus Type 2
  Varicella Zoster Virus
  Less Common Causes of Viral Meningitis
  Human Immunodeficiency Virus
  Approach to Patients With Viral Meningitis
VIRAL ENCEPHALITIS
  Herpes Simplex Virus
  Varicella Zoster Virus
  West Nile Virus
  Other Arthropod-Borne Viruses
  Rabies Virus
  Other Viruses
  Viral Encephalitis in Immunocompromised Patients
  Progressive Multifocal Leukoencephalopathy
  Approach to Patients With Viral Encephalitis
PRION DISEASES
SARS-CoV-2
POSTINFECTIOUS COMPLICATIONS OF CENTRAL NERVOUS SYSTEM VIRAL INFECTION
  Autoimmune Encephalitis Following Herpes Simplex Encephalitis
  Postinfectious Encephalomyelitis
  Acute Hemorrhagic Leukoencephalitis
  Transverse Myelitis
  Approach to Patients With Postinfectious Neurologic Injury

Invasion of the central nervous system (CNS) by viruses typically produces a meningoencephalitis in which either meningitis or encephalitis may predominate. Viruses may also infect cranial or spinal blood vessels leading to ischemic injury. Systemic or CNS infection by viruses or other infectious agents may elicit a host immune response that is cross-reactive with components of neural tissue, resulting in autoimmune encephalitis, demyelinating or hemorrhagic encephalomyelitis, transverse myelitis, injury to peripheral nerves, or optic neuritis. A few viruses, such as rubella, cytomegalovirus, or Zika virus may, in the course of maternal infection, cross the placenta to produce systemic fetal infection and CNS injury.

PATHOGENESIS OF VIRAL CENTRAL NERVOUS SYSTEM INFECTIONS

Before a virus can infect the CNS, it must first breach the cutaneous or mucosal barriers that protect the patient from the outside environment and then penetrate the blood—brain barrier to gain access to susceptible cells in the meninges, brain, or spinal cord. At each step, the virus must infect specific cell populations and produce progeny virus in order to continue the infection. Viruses can enter the body through ingestion, as in enterovirus infections; by the respiratory route, as in influenza or chicken pox; by inoculation across skin, as in arthropod-borne encephalitides or rabies; or across mucosal membranes, as in human immunodeficiency virus (HIV) infection. Virtually all viruses capable of infecting the CNS do so via hematogenous spread; exceptions are rabies virus and herpes simplex viruses types 1 and 2 (HSV-1, HSV-2), all of which travel from the periphery to the CNS within peripheral nerves. Varicella zoster virus (VZV) is transported within nerves during reactivated infection.

Infection at the cellular level may occur through several mechanisms. Herpesviruses are taken into the cell following fusion of the viral envelope to the host cell. The human polyomavirus, JC virus (JCV), the etiologic agent of progressive multifocal leukoencephalopathy (PML), binds to cellular serotonin and other receptors. Alphaviruses, such as St. Louis encephalitis virus, recognize

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cell surface laminin and heparan molecules. Viral replication within the host cell may result in various outcomes including lytic infection with cell death; productive infection with budding of viruses across the cell membrane without death of the host cell; or persistent infection, with the virus remaining latent over time. Classic examples of viruses causing latent infection include HSV-1, HSV-2, and VZV, all of which persist in sensory ganglia and may reactivate to cause several syndromes including cutaneous lesions and CNS disease.

Host response to viral infections initially involves innate immune responses and natural killer cells. Resolution of infection, however, involves both production of antibody and development of specific T-cell-mediated immune responses. Antibody is required to control and clear enteroviruses, and failure of antibody response may result in progressive enteroviral encephalitis. In contrast, immune control of West Nile virus (WNV) involves both B and T cells. Failure of host T-cell response is a major factor in the pathogenesis of PML, as is alteration in CNS T-cell immune surveillance following treatment with immunomodulatory agents such as natalizumab or brentuximab vedotin. $CD8^+$ T cells are important in maintaining HSV and VZV in their latent states and in controlling both primary and reactivated infection. In general, the host immune response is protective, although the inflammatory process that results may augment cerebral edema; however, CNS or systemic infections may also elicit an immune response cross-reactive with antigens to the central or peripheral nervous system, leading to postinfectious neurologic injury.

VIRAL MENINGITIS

Acute viral meningitis is most commonly a disease of children and young adults and is the most frequent CNS complication of viral infection. Viral meningitis accounts for an estimated 400,000 hospitalizations yearly in the United States; studies from Great Britain give an annual incidence of 2.73 per 100,000 population. Major causative agents in Western countries are enteroviruses (accounting for up to 77% of cases), HSV-2 (10 to 20% of cases), and VZV (10 to 20% of cases) (Table 42-1).[1] A minority of cases are caused by WNV or other arthropod-borne agents, HIV, HSV-1, lymphocytic choriomeningitis virus (LCMV), mumps virus, or other agents. In northern Europe, cases may be associated with tick-borne encephalitis virus and in southern Europe with Toscana virus. In Asia, Japanese encephalitis virus is a common etiologic agent for meningitis as well as encephalitis. In 35 to 50 percent of cases, no agent is identified.

The clinical presentation of viral meningitis in adults is similar to that of bacterial meningitis, although patients usually are less acutely ill (Table 42-2).[1] Onset of meningeal symptoms may be preceded by fever and other symptoms of systemic illness, but viral meningitis often is of abrupt onset with severe headache and nuchal rigidity. Although headache is most commonly the presenting symptom, it may be not be evident in infants and may be less prominent in young children and immunosuppressed individuals. Patients may exhibit photophobia, nausea, vomiting, and, in some cases, irritability and lethargy. Progression to obtundation or coma is rare without accompanying encephalitis. Some patients may have evidence of systemic viral infection such as pharyngitis or rash, but abnormalities on general physical examination are often absent. Meningeal signs are typically less severe than in bacterial meningitis and may be subtle. The neurologic examination otherwise is usually unremarkable, and the presence of focal neurologic signs should raise concern that some other process is present.

Enteroviruses

Enteroviruses are unenveloped single-stranded RNA viruses forming a genus in the family picornavirus. They account for 60 to 80 percent of cases of viral meningitis in which an agent is identified. Enteroviruses survive well in water and sewage, are transmitted by fecal–oral or hand–mouth routes, and replicate initially in the gastrointestinal tract. Enteroviruses were previously subdivided into three groups: polioviruses, echoviruses, and coxsackieviruses. Newer isolated enteroviruses have been assigned numbers (e.g., enterovirus 71 or EV71). Coxsackievirus A9 and echoviruses E7, E9, E11, E19, and E30 have accounted for 70 percent of all cultured isolates from cerebrospinal fluid (CSF) in cases of enteroviral meningitis. Polioviruses have been largely eradicated, persisting only in Nigeria, Pakistan, and Afghanistan. Other enteroviruses have a worldwide distribution, and although cases of enteroviral meningitis occur throughout the year, infection is most likely to occur during summer and early fall months when conditions of sanitation are most lax. Acute enterovirus infection is usually asymptomatic or may result in mild gastroenteritis or pharyngitis; less than 5 percent of patients will develop meningitis or encephalitis.

TABLE 42-1 ■ Major Viral Agents Associated With Human Neurologic Disease

Viruses	Genus (Family)	Animal Reservoir	Transmission	Geographic Location	Peak Season[a]	Neurologic Syndromes	Acute Diagnosis[b,c]	Treatment
Major Viruses in North America and Europe								
Coxsackieviruses Echoviruses Enterovirus 71 and other numbered enteroviruses	Enteroviruses (Picornaviridae)	No	Fecal–oral spread	Worldwide	Summer to early autumn	Meningitis (Encephalitis)[d] (Poliomyelitis) (Acute flaccid myelitis)	CSF PCR	Supportive (Pleconaril)[e]
Herpes simplex virus type 1 (HSV-1)	Herpesviruses (Herpesviridae)	No	Human contact	Worldwide	No seasonal distribution	Encephalitis	CSF PCR	Acyclovir
Herpes simplex type 2 (HSV-2)[f]	Herpesviruses (Herpesviridae)	No	Human contact	Worldwide	No seasonal distribution	Meningitis Recurrent meningitis Myelitis	CSF PCR	Acyclovir[g]
Varicella-zoster virus	Herpesviruses (Herpesviridae)	No	Respiratory or human contact	Worldwide	No seasonal distribution	Shingles Postherpetic neuralgia Meningitis Vasculitis involving brain, spinal cord, eye, peripheral nervous system (Encephalitis)	CSF PCR (acute infection) CSF IgM and IgG (reactivated infection)	Acyclovir Valacyclovir[g]
Cytomegalovirus[h]	Herpesviruses (Herpesviridae)	No	Human contact	Worldwide	No seasonal distribution	Encephalitis (infants or immune-compromised patients)	CSF PCR	Ganciclovir (Foscarnet)
Human herpesvirus 6[i]	Herpesviruses (Herpesviridae)	No	Human contact	Worldwide	No seasonal distribution	Meningitis Encephalitis	CSF PCR	Ganciclovir, Foscarnet
West Nile virus	Togaviruses (Flaviviridae)	Birds, esp. crows, jays, magpies	Mosquito sp. Organ transplantation	USA excepting Alaska and Hawaii[j]	Summer to early autumn	Meningitis Encephalitis Poliomyelitis	CSF IgM	Supportive
St. Louis encephalitis virus	Togaviruses (Flaviviridae)	Small mammals	Mosquito sp.	USA excepting Alaska and Hawaii	Summer to early autumn	Meningitis Encephalitis	CSF IgM	Supportive
Eastern equine encephalitis virus	Alphavirus (Togaviridae)	Salt marsh and other birds	Mosquito sp.	Atlantic seaboard, Gulf coast, upper Midwest	Summer to early autumn	Meningitis Encephalitis	CSF IgM (PCR)	Supportive
California/La Crosse virus[i]	(Bunyaviridae)	Small mammals	Mosquito sp.	USA, esp. Midwestern and mid-Atlantic states	Summer to early autumn	Meningitis Encephalitis	CSF IgM	Supportive
Colorado tick fever	Orbivirus (Reoviridae)	Small mammals	Tick sp.	Western USA (esp. mountain states), western Canada	Spring to mid-summer	Meningitis Encephalitis	PCR CSF IgM	Supportive

(Continued)

TABLE 42-1 ■ (Continued)

Viruses	Genus (Family)	Animal Reservoir	Transmission	Geographic Location	Peak Season[a]	Neurologic Syndromes	Acute Diagnosis[b,c]	Treatment
Lymphocytic choriomeningitis virus (LCMV)[k]	Arenavirus (Arenaviridae)	Mice (Hamsters)	Aerosol	Worldwide	Autumn to winter	Meningitis Encephalitis	PCR CSF IgM Serum and CSF IgM and IgG	Supportive
HIV1, (HIV2)	Human immunodeficiency virus (Retroviridae)	None	Intimate sexual contact; IV drug abuse	Worldwide	No seasonal distribution	Meningitis acutely. See Chapter 43	PCR Serology	ART
JC virus[h]	Polyoma virus (Polyomaviridae)	None	Unknown	Worldwide	No seasonal distribution	PML	PCR	Supportive[i]
Viruses Which Are Uncommon in North America but May Be Seen in Individuals Exposed in Endemic Areas								
Mumps virus[m]	Rubalavirus (Paramixoviridae)	None	Respiratory spread	Worldwide	January to May	Meningitis Encephalitis	CSF PCR	Supportive
Toscana virus	Phlebovirus (Bunyaviridae)	Reservoir in nature unknown	Sand fly	Italy, other Mediterranean countries	May to September	Meningitis (Encephalitis)	CSF PCR	Supportive
Japanese encephalitis virus	Flavivirus (Flaviviridae)	Pigs, wild birds (herons)	Mosquito sp.	Southeast Asia and Far East	Following wet season: varies by country	Encephalitis	CSF IgM	Supportive
Nipah virus	Henipa-virus (Paramyxo-viridae)	Pteropid fruit bats	Consumption of food contaminated with infected bat saliva or urine Human-to-human	India Bangladesh Southeast Asia Indonesia Australia	No seasonal distribution	Encephalitis	PCR CSF IgM Serum Serology	Supportive
Venezuelan equine encephalitis	Alphavirus (Togaviridae)	Birds, small mammals	Mosquito sp.	South and Central America, Extreme southern United States	No seasonal distribution	Encephalitis (Meningitis)	PCR	Supportive
Tick-borne encephalitis virus	Flavivirus (Flaviviridae)	Birds, small mammals	Tick sp. Unpasteurized milk	Europe, former Soviet Union, Asia	April to November	Meningitis Encephalitis		Supportive
Chikungunya virus	Alphavirus (Flaviviridae)	Birds, small mammals, monkeys	Mosquito sp.	Africa, Asia, Europe, and the Indian and Pacific Oceans	Summer to early autumn	Encephalitis (Rare)	PCR CSF IgM	Supportive
Dengue virus	Flavivirus (Flaviviridae)	Predominantly humans (nonhuman primates)	Mosquito sp.	Essentially worldwide but most common in tropical regions	Summer to early autumn	Encephalitis (rare) Meningitis (rare) Myelitis (rare)	CSF IgM	Supportive

Zika virus	Flavivirus (Flaviviridae)	Predominantly humans Nonhuman primates Possibly other animal species	Mosquito sp.	Africa, Pacific Islands, South America	Summer to early autumn	Encephalitis (rare) Meningitis (rare) Guillain–Barre syndrome Transplacental infection with fetal anomalies	CSF IgM (serum IgM and IgG antibodies in women suspected of being pregnant)	Supportive
Rabies virus	Lissavirus (Rhabdoviridae)	Bats, skunks, foxes, raccoons Dogs where canine rabies vaccination not utilized	Animal bite Aerosol (organ transplantation)	Worldwide	No seasonal distribution	Encephalitis (“furious” or “dumb” rabies) Ascending motor paralysis[n]	CSF PCR Nuchal biopsy	Rabies immune globulin and immunization after bite Supportive after onset of illness

ART, Antiretroviral medications.

[a] Sporadic cases of many agents may occur outside peak season.

[b] Retrospective diagnosis may be made by comparing antibody titers in acute and convalescent sera or by comparing serum:CSF ratios of antibody against those of other agents.

[c] Diagnostic methods for common agents such as HSV-1, HSV-2, enteroviruses, West Nile virus, and varicella-zoster virus are readily available through many hospital and commercial laboratories. Advice concerning less usual infections may be obtained through the Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA 30333, phone: 800-232-4636 and through their Division of Preparedness and Emerging Infections: 404-639-0385.

[d] Less frequent forms of illness are shown in parentheses.

[e] Not available in the United States.

[f] HSV-2 meningitis may occur as a single event but may also be recurrent and is the major cause of Mollaret meningitis.

[g] Mild cases of HSV-2 meningitis may not require treatment. Severe HSV-2 meningitis may require treatment with acyclovir. Treatment of recurrent HSV-2 meningitis may employ valacyclovir.

[h] Immunocompromised patients.

[i] Predominantly an infection of children.

[j] West Nile virus also present in much of Europe, the United Kingdom, Egypt, Israel, Africa, India, and Western Asia.

[k] A murine virus. Infections also reported after exposure to infected pet hamsters.

[l] Treatment in AIDS involves suppression of HIV with ARVs; treatment in patients developing PML in the setting of natalizumab therapy (and possibly other monoclonal agents) has consisted of withdrawal of the monoclonal agent and plasma exchange to reduce circulating levels of the monoclonal.

[m] Previously one of the major causes of viral meningitis in the United States. Still a major cause of meningitis in countries where vaccination is not routine. Associated with occasional outbreaks of infection in unvaccinated individuals in the United States and Europe.

[n] Incubation period may be 3 or more years. Obtaining history of exposure should take this into account.

TABLE 42-2 ■ Signs and Symptoms of Viral Meningitis

Common
Headache
Fever
Nausea, vomiting
Stiff neck (not present in all cases; may be subtle)
Less Common
Lethargy, mild confusion, irritability*
Seizures*
Systemic signs including rash, diarrhea, pharyngitis, myalgias, adenopathy (with mumps: parotitis)

*Significant impairment in consciousness, seizures, and/or focal neurologic signs suggest the likelihood of encephalitis or other severe infection (meningitis, parameningeal infection, encephalitis).

Enteroviral CNS infection typically causes meningitis rather than encephalitis, with fever, headache, and stiff neck. These symptoms commonly last for 1 to 3 weeks in older children and adults. In occasional patients, enteroviruses may cause encephalitis or rarely a paralytic disease similar to polioviruses (see below) and may cause protracted, atypical infection in immunocompromised patients.

Herpes Simplex Virus Type 2

HSV-2 is a double-stranded DNA virus that is universal in human populations. HSV-2 is usually transmitted sexually, with antiviral antibodies first appearing in adolescence or early adult life. Following acute infection, the virus persists predominantly in spinal sensory ganglia and is subject to periodic reactivation, often without cutaneous or mucosal signs of infection. HSV-2 accounts for up to 10 to 20 percent of isolates in adults with viral meningitis and is roughly twice as common among women. HSV-2 as a cause of viral meningitis should be considered, particularly in young, sexually active adults. Older data suggested that up to 36 percent of women and 11 percent of men had headache, fever, or nuchal rigidity at the time of their first attack of genital herpes. Some patients with HSV-2 meningitis following genital herpes may have focal lumbosacral symptoms including urinary retention suggesting nerve root infection, and the virus may also be associated with myelitis. HSV-2 DNA can frequently be detected in CSF by amplification using the polymerase chain reaction (PCR). Approximately 20 percent of individuals with acute HSV-2 meningitis may subsequently develop recurrent episodes of meningitis (Mollaret meningitis). Many individuals with recurrent meningitis have no history of genital herpes and lack genital lesions during attacks of meningitis.

Patients with HSV-2 meningitis usually recover without treatment. Although successful treatment with acyclovir has been described in individual cases, the efficacy of antiviral therapy in acute or recurrent HSV-2 meningitis is uncertain. In one clinical trial, suppressive treatment with valacyclovir did not prevent recurrence of HSV-2 meningitis.[2]

Varicella Zoster Virus

VZV is a herpesvirus typically associated with chicken pox during acute infection and with cutaneous zoster (shingles) during reactivated infection. Like HSV-2, VZV is thought to account for 10 to 20 percent of identified cases of viral meningitis. Meningitis may occur during either primary or reactivated infection and may do so in the absence of rash. In contrast to many other viruses, VZV meningitis may result in significant CSF hypoglycorrachia and may be accompanied by a CSF pleocytosis characterized by atypical lymphocytes. As with HSV-2 meningitis, most immunocompetent patients with VZV meningitis recover without treatment. VZV infection may also produce a wide variety of other neurologic conditions, which are discussed in greater detail below.

Less Common Causes of Viral Meningitis

The arthropod-borne agents—WNV, St. Louis encephalitis virus, California encephalitis virus, Powassan virus, Jamestown Canyon virus, and Colorado tick fever virus—are most commonly associated with encephalitis, but may also cause meningitis. WNV, St. Louis encephalitis virus, Jamestown Canyon virus, and California encephalitis virus are transmitted by mosquitoes and tend to be more common in summer and early autumn months. The tick-borne agents Powassan virus and Colorado tick fever virus can cause a rash and most frequently occur during spring and early summer months. An important diagnostic consideration in patients with suspected Colorado tick fever is the tick-borne rickettsial illness Rocky Mountain spotted fever, which also has a peak incidence in spring and summer, usually has a rash, and requires antibiotic treatment.

LCMV is an arenavirus whose natural host is mice but which can cause meningitis and, less frequently, encephalitis in humans. The virus is present in mouse urine and is acquired by the respiratory route. At one time, it was thought to account for roughly 4 percent of diagnosed cases of viral meningitis, but in recent years it has become much less common, for unknown reasons. LCMV infections are classically most common in autumn and winter. Occasional outbreaks of infection have been associated with exposure to mice in animal facilities or to pet hamsters or guinea pigs. The meningitis associated with LCMV may be accompanied by low CSF glucose levels, which may persist over weeks to months in cases with prolonged recovery. In neonates, LCMV may cause a fatal systemic and CNS infection. Outbreaks of severe infection with high mortality have also been reported in which LCMV has been transmitted by organ transplantation. Reliable antiviral therapy for LCMV infection is not available; one patient with transplant-acquired LCMV infection recovered after reduction of the patient's immunosuppressive regimen and treatment with ribavirin.

Mumps virus, once a major cause of meningitis worldwide, is now rare in developed countries but remains a significant cause of meningitis in areas where mumps immunization is not practiced. The virus has also caused occasional epidemics in Western countries in unvaccinated populations exposed to individuals who have visited areas where mumps is still prevalent.

Human Immunodeficiency Virus

CNS invasion occurs early in the course of primary HIV infection, and meningitis due directly to HIV occurs in 9 to 24 percent of patients (see Chapter 43). The meningitis usually develops near the time of seroconversion and often occurs in the setting of an acute, mononucleosis-like retroviral syndrome characterized by fever, pharyngitis, and cervical lymphadenopathy; CNS findings of disorientation, confusion, or psychosis accompany this syndrome in some patients. Primary HIV meningitis should be considered in young adults with meningitis, particularly when they have HIV risk factors or a coexistent mononucleosis-like syndrome. The symptoms of meningitis are usually not severe and resolve in most but not all cases; in some patients, HIV meningitis becomes chronic. The CSF typically reveals a mild lymphocytic pleocytosis, mildly elevated protein content, and normal glucose level. HIV meningitis may be the initial presentation of HIV infection and may also occur early enough that standard serologic tests for HIV (as well as tests for home use) have not yet become positive. Initial diagnostic testing, per CDC recommendations, ideally involves a combined HIV-1/2 antigen/antibody assay; this should be repeated in 45 days if the assay is negative but there is high suspicion of HIV. Individuals testing positive should be assayed for viral load in serum and CSF. Treatment of HIV is with antiretroviral therapy, and follow-up assay for antiviral antibodies is used to confirm the diagnosis. In approaching patients with suspected HIV meningitis, it must be kept in mind that lymphocytic meningitis in patients with HIV infection may be caused by a wide variety of other agents, many of which are treatable.

Approach to Patients With Viral Meningitis

Bacterial meningitis is the primary concern in any patient presenting with acute meningitis. If the patient is severely ill, bacterial meningitis should be suspected and presumptive antibiotic therapy should be initiated immediately, usually along with corticosteroids.[3] Similarly, acyclovir should be initiated if HSV encephalitis is a significant diagnostic concern. Antibiotics and acyclovir can be discontinued once CSF studies are negative. In general, patients presenting with viral meningitis are less severely ill, and antibiotic and acyclovir treatment may often be deferred.

The diagnosis of viral meningitis is made by lumbar puncture and CSF analysis.[3] In acute bacterial meningitis, there is often an elevated opening pressure and typically a marked neutrophilic pleocytosis, with significantly elevated protein and depressed glucose concentrations. In contrast, in viral meningitis the opening pressure is usually normal or mildly elevated, and the CSF white cell count is usually in the range of 50 to 2000/mL. Although viral meningitis typically produces a lymphocytic pleocytosis, polymorphonuclear leukocytes may constitute over 50 percent of the cells during the first 24 to 36 hours of the infection and may occasionally remain the predominant cell type for longer periods of time. Protein is usually elevated in the range of 50 to 100 mg/dL but is sometimes higher. The CSF glucose level in viral meningitis is usually greater than 50 percent of blood glucose; the absence of CSF hypoglychorrachia is an important consideration in differentiating viral from bacterial meningitis. Depression of glucose to levels approaching those of bacterial meningitis may occasionally occur in meningitis caused by HSV-2, VZV, mumps, and LCMV. In the proper setting, lymphocytic pleocytosis with low CSF glucose may also raise concern about tuberculous or fungal meningitis.

Specific diagnosis of viral agents in CSF currently involves PCR amplification of viral RNA or DNA; at present, tissue culture isolation of virus is rarely performed for diagnostic purposes (Table 42-1). PCR is rapid and has a high level of sensitivity in meningitis due to enteroviruses, HSV-2, and VZV during acute infection. PCR can identify all strains of enteroviruses but does not distinguish between individual strains. Enteroviral RNA can be identified in CSF in the first 1 or 2 days of meningitis, from throat for several days, and from stool for a few weeks. Because asymptomatic enterovirus infections are common in the summer months, enterovirus isolation from throat or stool does not make a definitive diagnosis of enterovirus meningitis. Use of an enterovirus PCR assay in the emergency department in children with aseptic meningitis has resulted in significantly less antibiotic use, shorter length of hospitalization, and lower hospital costs. Film-based multiplex assays, capable of detecting nucleic acids of multiple infectious agents provide rapid screening but should be followed up with conventional PCR. Although CSF PCR is the diagnostic study of choice in many viral meningitides, the assay may be negative early in the disease course, and diagnostic yield may be highest when CSF is obtained within 3 to 14 days of onset of meningitis. In certain instances, the detection of CSF immunoglobulins may have greater diagnostic sensitivity than PCR. This is the case in WNV neuroinvasive disease and other arbovirus infections, in which detection of virus-specific immunoglobulin M (IgM) is more sensitive than PCR. Similarly, detection of virus-specific immunoglobulin G (IgG) in CSF may prove diagnostic in infections due to protracted or reactivated VZV where PCR is negative. Identification of the causative agent in viral meningitis may be made retrospectively by detecting a rise in IgG antibody titers between acute and convalescent (obtained after 3 to 6 weeks) serum or, at times, by detecting an abnormal serum:CSF ratio of antiviral antibodies.

Other laboratory studies in viral meningitis are usually unhelpful. Peripheral white blood cell count may be normal or elevated. Computed tomography (CT) scans and magnetic resonance imaging (MRI) of the brain are typically normal. The electroencephalogram (EEG) is usually normal but may occasionally show mild background slowing. Marked asymmetries or seizure foci should not be seen unless encephalitis predominates.

Viral meningitis is sometimes referred to by the older term "aseptic meningitis." This term, however, subsumes a broad range of clinical entities characterized by a meningeal reaction but distinct from purulent bacterial meningitis. It may include not only viral meningitis but also infections by bacteria that are not readily detected in routine cultures (*Leptospira icterohaemorrhagiae*, *Borrelia burgdorferi*, *Treponema pallidum*, *Mycoplasma pneumoniae*), meningeal involvement by *Rickettsia*, *Ehrlichia*, or *Anaplasma*, and infection by parasites such as *Toxoplasma gondii*. The possibility of infection by one of these agents should be kept in mind in a patient with suspected viral meningitis, since all are amenable to antibiotic treatment. In particular, *B. burgdorferi* can be a major cause of lymphocytic meningitis in endemic areas (see Chapter 39). Aseptic meningitis may also be associated with a variety of pharmacologic agents including nonsteroidal anti-inflammatory agents, trimethoprim-sulfamethoxazole, augmentin, carbamazepine, intravenous immunoglobulin G, and the murine monoclonal antibody OKT3. Treatment of viral meningitis is supportive in most cases. Analgesics may be required for individuals with severe headaches, and antiemetics for those with considerable nausea and vomiting. Hospitalization is seldom required except when vomiting is severe enough to cause dehydration or when bacterial meningitis cannot be excluded. Acyclovir and valacyclovir have been used to shorten the duration of illness in acute meningitis due to HSV-2 and VZV. However, controlled studies do not exist, and no standardized regimen has been developed. Patients with recurrent HSV meningitis may wish to keep oral acyclovir or valacyclovir at home and take the drug at the onset of meningeal symptoms. Ongoing twice daily treatment with valacyclovir at a dose of 0.5 mg has not been shown to prevent recurrence, but higher dosages have not been formally studied. The antiviral agent pleconaril, which prevents uncoating of viral RNA, has been used in enteroviral meningitis but is not routinely available in the United States.

As a group, patients with viral meningitis generally make a complete recovery within 1 to 2 weeks. Not all patients recover this quickly, however, and symptoms such as fatigue may last for weeks or even months. CSF abnormalities may also persist for well beyond the initial period of recovery. In addition, there have been occasional reports of permanent sequelae, usually but not always in small children, including cognitive impairment, deafness, and cranial nerve palsies. Aqueductal stenosis with hydrocephalus is a rare complication of HSV-2 and mumps meningitis.

VIRAL ENCEPHALITIS

Viral encephalitis represents viral infection of cells within the brain parenchyma, and signs and symptoms reflect this involvement (Table 42-3)[4]. The cell populations in which viral replication occurs differ among the various viruses and may involve neurons, glia, or, at

TABLE 42-3 ■ Signs and Symptoms of Viral Encephalitis

Common
Impairment of consciousness: confusion, lethargy, delirium, coma
Inability to recall new information/anterograde amnesia (esp. HSV-1 encephalitis)
Headache
Fever
Stiff neck (may be subtle)
Less Common
Focal or generalized seizures
Hemiparesis, spasticity, or other signs of focal CNS dysfunction including aphasia, blindness, or ataxia
Cranial nerve palsies
Tremors

HSV, herpes simplex virus; CNS, central nervous system.

times, vascular endothelial cells. The result of the infection may be death of specific cell populations or more widespread destruction involving multiple cell types. Viruses affecting unique populations of cells include rabies, which infects neurons exclusively; poliomyelitis, which involves spinal and other motor neurons; and JCV, which causes lytic infection almost exclusively in oligodendrocytes. Viruses infecting multiple cell types, often with extensive parenchymal destruction, include HSV and agents of the arthropod-borne encephalitides. Parenchymal destruction in severe infections such as herpes simplex encephalitis may be accompanied by hemorrhage. Virtually all viral encephalitides are accompanied by some degree of meningeal inflammation and cerebral edema, the latter of which may be severe enough to cause death.

Viral encephalitis occurs worldwide, with a particularly high incidence in the tropics. Table 42-1 outlines the major viruses that cause encephalitis and lists some of their distinguishing characteristics. Each year in the United States, between 1,000 and 5,000 cases of encephalitis are reported to the Centers for Disease Control and Prevention (CDC). Identification of the etiologic agent in viral encephalitis is achieved in only about 50 percent of cases.

Herpes Simplex Virus

Herpes simplex encephalitis represents only 10 to 15 percent of cases of viral encephalitis in the United States. However, it remains the most common cause of fatal nonepidemic viral encephalitis and is the only viral encephalitis for which effective antiviral therapy has been proven in clinical trials.[4,5] HSV is ubiquitous in human populations. HSV-1 is most commonly acquired in early childhood as a gingivostomatitis which may be either symptomatic or asymptomatic. HSV-2 is more commonly sexually transmitted and is classically acquired during adolescence or adulthood. Both agents enter neuronal processes during primary infection and persist in neurons within sensory ganglia. HSV-1, which may also persist within the CNS, is responsible for the majority of cases of herpes simplex encephalitis in adults; of these cases, roughly two-thirds represent reactivated infection. Although HSV-2 has traditionally been associated with meningitis and, less frequently, myelitis, it may also be isolated from cases of herpes simplex encephalitis.

The pathogenesis of herpes simplex encephalitis is not well understood. Encephalitis has been postulated to follow the spread of virus from the trigeminal ganglia through sensory fibers to the meninges overlying the temporal lobes and orbitofrontal cortex or, alternatively, to follow reactivation of virus in the olfactory bulbs prior to spread to the brain itself. HSV infects neurons, glia, and ependyma.

Herpes simplex encephalitis occurs throughout the year without seasonal incidence, affects men and women equally, and may occur at any age. Immunosuppression does not increase the risk of encephalitis, but the course of encephalitis may be atypical in these individuals. The virus has a predilection for orbitofrontal cortex and temporal lobes, which it may involve unilaterally or bilaterally. The cingulate cortex is also involved in many patients. Occasionally herpes simplex encephalitis involves the occipital cortex or brainstem, in rare cases without temporal lobe involvement. Vascular congestion and petechial or larger hemorrhages may be present; progression of the infection results in extensive and frequently hemorrhagic destruction of brain.

Herpes simplex encephalitis presents with an almost universal triad of headache (in over 90% of cases), fever, and alteration in mental state. Changes in mental state at presentation may range from confusion, frank psychosis, or somnolence to stupor or coma. Temporal lobe involvement may be manifested by olfactory or gustatory hallucinations, déjà vu phenomena, and upper quadrant visual field defects. Bilateral temporal involvement may result in the loss of ability to store and recall new information, and involvement of the dominant hemisphere can result in aphasia. Rare patients present with symptoms and signs referable to the occipital lobes. Focal or generalized seizures may occur at any point during the acute illness or after recovery.

The CSF typically contains a lymphocytic pleocytosis of 50 or more cells/mm^3 (median, 130 cells/mm^3). In occasional patients, however, the cell count is normal. Although herpes simplex encephalitis is frequently hemorrhagic, the presence or absence of red blood cells in CSF does not differentiate HSV infection from encephalitis due to other causes. CSF protein concentration has a median value of 80 mg/dL, but ranges from normal to over 700 mg/dL; CSF glucose is usually normal. MRI with gadolinium enhancement is the initial diagnostic procedure of choice and will usually demonstrate hyperintense T2-weighted signal along with gadolinium enhancement within the temporal lobe; it may also show involvement of the insula, orbitofrontal cortex, and cingulate gyrus (Fig. 42-1). MRI abnormalities in other regions of cortex or brainstem, without temporal lobe involvement, do not exclude the diagnosis. The EEG may show temporal lobe slowing or spike-wave activity. CT with contrast and EEG are less sensitive, but used together may provide diagnostic information when MRI is not available.

A specific diagnosis of herpes simplex encephalitis is made by amplification of viral DNA from CSF using PCR. The overall diagnostic accuracy of PCR in patients with brain biopsy-proven HSV encephalitis is 98 percent. Rapid provisional diagnosis may be achieved by film array methods, but these should be confirmed with more traditional PCR. In some patients, PCR may be negative at presentation due to low copy numbers of DNA in the CSF; in these cases, repeat CSF PCR after 4 to 7 days is usually positive. The diagnostic yield of PCR falls to 21 percent in patients after 2 weeks of antiviral treatment. Determination of acute antibody titers is not of value in the acute diagnosis of HSV encephalitis; however, comparison of acute and convalescent serum titers may be useful retrospectively and, in rare cases, provides diagnostic information when PCR was negative or when CSF was not obtained initially. Retrospective serologic confirmation of herpes simplex encephalitis may also be made by determining serum:CSF ratios of HSV-specific antibodies to identify intrathecal antibody production.

Herpes simplex encephalitis is treated with intravenous acyclovir (Table 42-4), which inhibits HSV

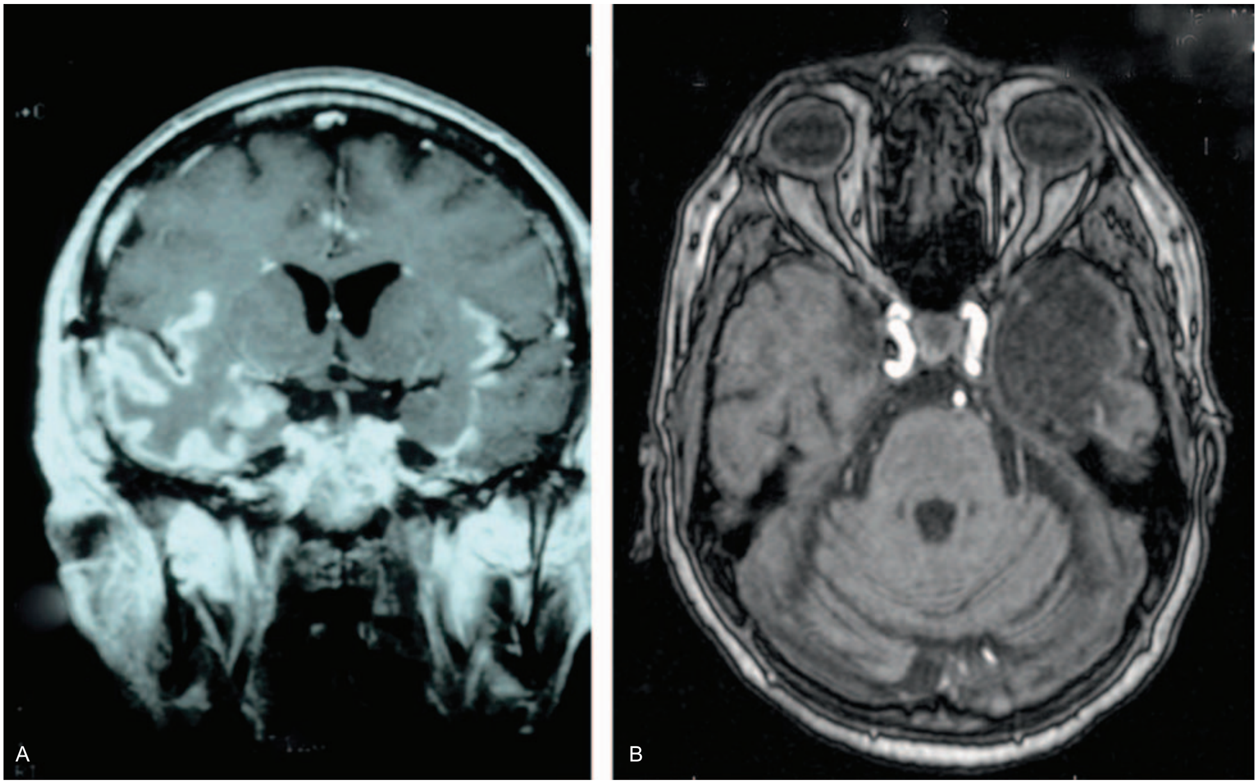

FIGURE 42-1 ■ *A*, Magnetic resonance imaging (MRI) of herpes simplex virus encephalitis. T2-weighted fluid-attenuated inversion recovery sequence showing increased signal in right temporal lobe, insula, and orbitofrontal cortex. There is also involvement of the left insula. *B*, T1-weighted MRI 6 months after infection, showing massive destruction of the left temporal lobe.

TABLE 42-4 ■ Antiviral Agents Used for CNS Infections

Antiviral	Mechanism of Action	Indication	Regimen in Adults	Major Adverse Effects
Acyclovir	Competes with deoxyguanosine triphosphate as a substrate for DNA polymerase. Causes viral DNA chain termination. Converted to active form in infected cells	HSV encephalitis Severe HSV meningitis VZV encephalitis, CNS vasculitis, or severe meningitis	10 mg/kg IV every 8 h × 21 days	Nephrotoxicity: may cause renal failure if patient not adequately hydrated Psychosis Stevens–Johnson syndrome Tissue necrosis
		Recurrent HSV-2 meningitis	800 mg 5×/day for 5–7 days given orally	
		Varicella (chicken pox) or herpes zoster (shingles)	800 mg 5×/day for 5–7 days given orally	
Valacyclovir	Same as acyclovir	HSV meningitis (esp. recurrent)	1000 mg every 8 h for 7 days	Similar to acyclovir
		Herpes zoster (shingles)	1000 mg every 8 h for 7 days	
Ganciclovir	Similar to acyclovir: inhibits viral DNA polymerization	Encephalitis due to cytomegalovirus or HHV-6	5 mg/kg every 12 h for 14–21 days	Hematologic toxicity (anemia, leukopenia, thrombocytopenia) Nephrotoxicity: may cause renal failure if patient not adequately hydrated
Foscarnet	Selective inhibition of viral DNA polymerase	Encephalitis due to cytomegalovirus or HHV-6; acyclovir resistant VZV	90 mg/kg IV every 12 h for 14–21 days	Hematologic toxicity (anemia, leukopenia, thrombocytopenia) Nephrotoxicity: may cause renal failure if patient not adequately hydrated

synthesis by competing with deoxyguanosine triphosphate as a substrate for DNA polymerase and causing DNA chain termination. The drug is converted into its pharmacologically active monophosphate form by virally encoded thymidine kinase and thus only becomes active in infected cells. Acyclovir is administered intravenously at 10 mg/kg body weight every 8 hours for 21 days. Complications of acyclovir therapy are usually mild. The major concern is nephrotoxicity due to deposition of drug crystals, which can be avoided by careful hydration. Although acyclovir resistance has been reported in other conditions, acyclovir-resistant herpes simplex encephalitis is rare.

Prior to the introduction of acyclovir, overall mortality from herpes simplex encephalitis was over 70 percent, with mortality approaching 100 percent in patients over the age of 40 years.[5] The advent of acyclovir has reduced the overall mortality to 28 percent, and instituting antiviral therapy at presentation when the diagnosis is suspected has reduced 1-year mortality to 14 percent. Patients who are alert or lethargic when treatment is initiated have an excellent likelihood of survival, but mortality in patients treated when comatose still approaches 25 percent. The likelihood of death or serious neurologic impairment is greater when the patient is elderly, initiation of acyclovir treatment is delayed, or evidence of extensive CNS involvement is present on initial neuroimaging. Even with prompt initiation of treatment, up to two-thirds of patients are left with permanent neurologic deficits including epilepsy, impaired cognition, aphasia, anterograde amnesia, or motor deficits. Neurologic improvement takes place over months, and some patients who are severely impaired immediately after treatment may have a good functional recovery over time. In roughly one-quarter of patients, apparent recovery from HSV encephalitis may be followed by apparent clinical relapse. Although late neurologic symptoms may occasionally be due to recurrent viral infection,[6] clinical worsening in most cases does not represent viral recrudescence but rather postinfectious autoimmune injury due to antibodies directed against neuronal *N*-methyl-D-aspartate or, less often, GABA_A receptors (NMDAR; $\text{GABA}_\text{A}\text{R}$).[7] Antibody-mediated encephalitis as a consequence of HSV encephalitis is discussed in greater detail below.

Varicella Zoster Virus

VZV, like HSV, is an enveloped double-stranded DNA virus that is worldwide in distribution. The virus is acquired by the respiratory route and replicates initially in tonsillar tissue to produce a viremia followed by seeding of multiple tissues including skin. Primary infection classically results in chicken pox, but individuals may also be infected acutely with little or no rash. The virus is then taken up by nerves supplying infected skin or other tissues and is transported to sensory ganglia, establishing lifelong persistence. VZV thus differs from HSV in that it produces an acute viremic illness and only then persists secondarily and spreads within neurons. Viral latency in sensory ganglia is heavily controlled by T-cell-mediated immunity, and reactivation of infection may occur with waning of immune response during old age or in states of compromised host immunity.

Cutaneous zoster (shingles), the most common manifestation of reactivated VZV infection, affects roughly 1 million adults in the United States annually.[8] The likelihood of developing zoster is higher in individuals who acquired chicken pox during infancy. Most cases of zoster occur in patients older than 50 years. Neuropathologic correlates of cutaneous zoster include focal meningeal inflammation, necrosis of associated neurons, and degeneration of motor and sensory nerve roots in the involved area. Cutaneous zoster may develop without known precipitating cause or may be triggered by systemic cancer, spinal irradiation, HIV infection or other immunosuppressed states, or spinal trauma. Many patients experience a sharp, burning discomfort in a dermatomal distribution for 2 to 5 days before onset of the rash. A localized redness with red macules then develops and progresses to vesicles in the same dermatomal pattern as the pain. Additional vesicles may appear over the next 2 to 7 days. The distribution of herpes zoster is usually unilateral and involves a single dermatome. The rash involves the trunk in 50 percent, the head in 20 percent, the arms in 15 percent, and the legs in 15 percent of cases. Over the next month, the dermatomal pain slowly disappears, leaving residual hypoalgesia or hyperalgesia. Occasional patients may present with dermatomal pain without rash, termed *zoster sine herpete*. Treatment with oral valacyclovir (1 g three times daily for 7 to 10 days) shortens the duration of rash and acute pain. Recommended treatment in immunocompromised individuals is 5 to 10 mg/kg of usually intravenous acyclovir given three times daily for 5 to 7 days.

Postherpetic neuralgia (PHN)—pain occurring in the distribution of the original rash and persisting for longer than 3 months—occurs in 9 to 14 percent of patients following shingles and increases with advancing age.[8] The pain may be relentless, episodic, or paroxysmal and may be elicited by cutaneous contact or stimulation. Postherpetic itch is also common. Two vaccines are in use to prevent VZV infection. The live attenuated Oka strain VZV vaccine (Zostavax®), introduced in 2006, has been shown to reduce the incidence of cutaneous zoster in healthy individuals by 50 percent and the incidence of PHN by 67 percent. The newer recombinant Shingrix® vaccine, introduced in 2017, reduces the incidence of both shingles and PHN by over 90 percent and is preferred in most patients. To what extent antiviral treatment of acute zoster lessens the likelihood of PHN has not been clearly demonstrated. Symptomatic treatment of PHN is often disappointing. Tricyclic antidepressants, gabapentin, pregabalin, duloxetine, controlled-release morphine sulfate, oxycodone, and lidocaine patches have moderate to high efficacy, but are sometimes completely unhelpful, as are a variety of approaches including nerve stimulation and botulinum toxin. Aspirin in cream or ointment form, topical capsaicin, and intrathecal methylprednisolone are less effective, limited by side effects, or both. For most of these medications, treatment involves escalating dosages of medication until pain relief is achieved or unacceptable side effects occur.

VZV may invade the CNS during primary or reactivated infection and, in reactivated infection, may do so in the absence of cutaneous zoster.[8] Prior to the advent of PCR testing, CNS invasion by VZV was considered unusual. It is now realized, however, that CNS involvement by VZV is much more frequent; in one series VZV was found to be the most common agent identified in viral meningitis and encephalitis (nearly 30% of isolates). Studies from France and England have identified the agent in 5 to 15 percent of encephalitis isolates. The virus is now known to cause a wide range of syndromes of neurologic injury involving not only brain and spinal cord but also cranial nerves and brainstem or peripheral ganglia. CNS invasion in reactivated VZV infection occurs following the spread of virus from trigeminal or spinal sensory ganglia; in this process, the virus may produce ophthalmic involvement or may produce Ramsay–Hunt syndrome, in which infection of the tympanic membrane and surrounding structures is accompanied by facial nerve palsy. Of greater concern and unlike HSV, VZV may infect both large and small vessels supplying the brain or spinal cord, at times followed by spread of the infection into neural parenchyma. Involvement of vessels may produce focal or multifocal ischemic injury or may cause vessel-wall necrosis with resulting arterial dissection, aneurysm formation, or hemorrhage within the subarachnoid space or brain parenchyma. An association of VZV with giant cell or temporal arteritis has been reported, but the association between these two entities is still disputed.[8]

The classic presentation of VZV vasculopathy is herpes zoster ophthalmicus, in which there is initial superficial zoster in the distribution of the ophthalmic branch of the trigeminal nerve followed days to weeks later by stroke in the territory of the carotid or middle cerebral artery. However, VZV vasculitis may occur with or without preceding cutaneous zoster or herpes zoster ophthalmicus or oticus and may involve virtually any vascular territory within the brain or spinal cord. VZV vasculitis may be significantly more severe in HIV infection or other immunosuppressed states, and immunosuppressed patients may develop a more slowly progressive CNS vasculopathy or myelitis.[8]

CSF in acute VZV CNS infection may reveal a mononuclear pleocytosis, at times with red blood cells and sometimes hypoglycorrhachia. VZV encephalitis in the setting of acute VZV infection may be diagnosed by PCR; however, the reaction rapidly becomes negative, so that a negative PCR does not exclude the diagnosis. Diagnosis of VZV vasculopathy in the setting of reactivated infection is made by the presence of elevated titers of anti-VZV IgG antibodies in CSF. Oligoclonal bands are commonly present and are reactive with VZV proteins.

Treatment of VZV encephalitis is with acyclovir, 10 mg/kg, usually intravenously, every 8 hours for a minimum of 14 days. Oral prednisone, 1 mg/kg, given daily for 5 days, may be used to treat the inflammatory component of the vasculitis; more prolonged treatment is avoided to prevent steroid-induced immunosuppression.

West Nile Virus

WNV, a single-stranded RNA flavivirus virus, is currently the most common cause of epidemic encephalitis in the United States.[4,9] The virus infects multiple species of animals and birds, in particular crows, jays, magpies, and ravens. *Culex* species mosquitoes, predominantly *C. tarsalis* and *C. pipiens*, are the primary vectors for human infection. WNV produces infection predominantly in the summer and early autumn, when mosquitoes are most active. WNV causes infections nationwide (Fig. 42-2). Of reported cases, nearly two-thirds represent neuroinvasive disease. As of November 2019, 872 cases had been reported for the year (Fig. 42-2) with 570 neuroinvasive cases and 46 deaths (Fig. 42-3). In most individuals, WNV infection is silent or produces only trivial symptoms. In 20 percent of infected patients, symptomatic West Nile fever develops, characterized by malaise,

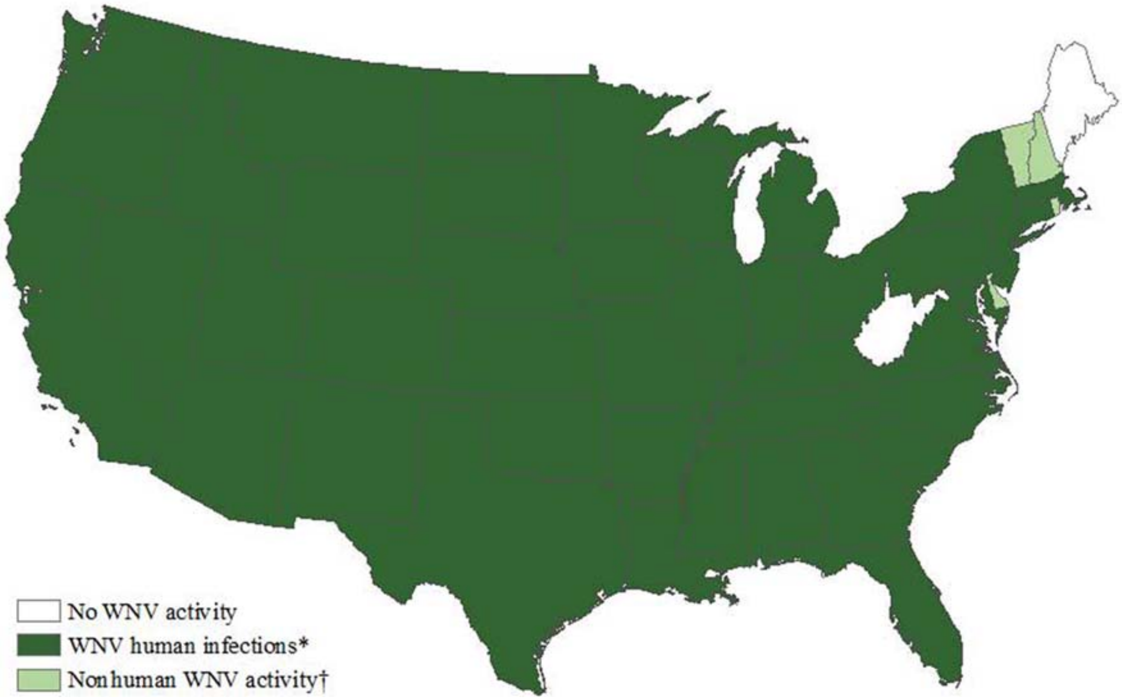

FIGURE 42-2 ■ Distribution of West Nile virus in the United States: Human and animal cases as of November, 2019. (From the US Centers for Disease Control and Prevention.)

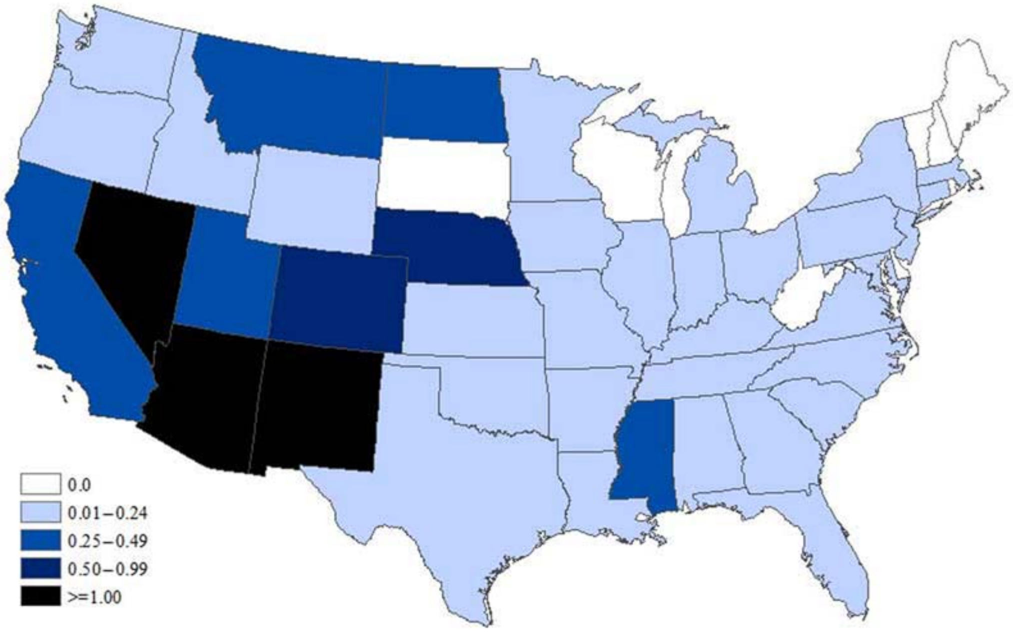

FIGURE 42-3 ■ Distribution of cases of West Nile neuroinvasive disease in the United States, 2019. (From the US Centers for Disease Control and Prevention.)

fatigue, anorexia, headache, nausea, vomiting, myalgia, fever, eye pain, and a nonspecific maculopapular rash. The illness usually lasts less than 7 days, although a minority of patients may remain symptomatic for as long as 6 weeks.

Less than 1 percent of infected patients develop neuroinvasive disease, which is more common in the elderly and is especially severe in immunosuppressed patients or transplant recipients. West Nile encephalitis typically presents with fever, headache, and altered mental state, stupor, or coma. Other signs of parenchymal involvement may include cerebellar ataxia or movement disorders including tremor, myoclonus, and parkinsonian symptoms. WNV infection may also result in a syndrome of acute flaccid paralysis similar to that seen with polio virus or Japanese encephalitis virus infection. A minority of patients develop chorioretinitis or vitritis. CSF in neuroinvasive WNV infection typically shows a mild elevation in opening pressure, lymphocytic pleocytosis, mild elevation of protein level, and normal glucose concentration. CSF white blood cell count is usually 50 to 260 cells/mm^3 but may be as high as 2,600 and may be heavily polymorphonuclear, in particular at presentation. In one series, the cell count was normal in 20 percent of patients. Occasional patients have low serum sodium levels indicative of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). MRI is often normal, although a minority of patients have areas of increased signal on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences in the substantia nigra, basal ganglia, and thalamus. Patients with WNV-induced flaccid paralysis may show increased signal in the anterior horns of the spinal cord. A single, acute, CSF specimen positive for WNV-specific IgM antibodies is diagnostic of WNV neuroinvasive disease. PCR is less reliable. Paired sera positive for WNV-specific IgM antibodies (a fourfold or greater rise in titer from the "acute" serum, obtained 0 to 7 days after symptom onset, and the "convalescent" serum, obtained 14 to 21 days after symptom onset) also provide serologic confirmation.

Treatment of WNV encephalitis is currently supportive. A multicenter controlled trial of human intravenous IgG containing high titers against WNV did not show an effect on the disease. Prognosis for recovery after WNV meningitis or encephalitis is good, although recovery may be extremely prolonged. The likelihood of complete recovery after West Nile flaccid paralysis is poor.

Other Arthropod-Borne Viruses

Several arthropod-borne viruses other than WNV may infect humans and cause neurologic disease. All but two of the agents occurring in the United States and Canada are carried by mosquitoes, with rates of infection that peak in mid-summer through early autumn.

Colorado tick fever virus and Powassan virus are carried by ticks, and infections caused by these agents tend to occur in late spring and early summer. Prior to the advent of WNV in the United States, St. Louis encephalitis was the most common arthropod-borne cause of encephalitis. Eastern equine encephalitis, although rare, remains the most deadly and outbreaks have recently occurred. No human case of Western equine encephalitis virus infection has been reported since 1994.

St. Louis encephalitis virus, like WNV, is a mosquito-borne virus that is a member of the family Flaviviridae. Cases of St. Louis encephalitis have been reported from almost every area of the United States, but the majority occur in the central Midwest and Texas. The virus is usually seen with scattered rural infections but may also cause urban epidemics. St. Louis encephalitis resembles neuroinvasive West Nile disease but rarely if ever produces a flaccid, polio-like illness. The two diseases are both more severe in the elderly and they have similar CSF findings. Diagnosis of St. Louis encephalitis is either by CSF IgM, by a rise in antibody titers, or both.

Eastern equine encephalitis virus is an agent of wading and migratory birds that is found predominantly along the Atlantic seaboard, the Mississippi valley, the Gulf of Mexico, Michigan, and Wisconsin. Although the virus does not usually produce severe infection in its natural hosts, it can cause lethal infection in horses and may cause epizootic outbreaks of infection in flocks of turkeys or in exotic or game farm birds. The virus is most apt to cause encephalitis in infants and in individuals over 55 years of age. A prodromal illness which may include fever, headache, and abdominal pain frequently occurs. Onset of encephalitis may be fulminant: nearly 70 percent of patients present in stupor or coma, and presentation only with meningeal symptoms is uncommon. Corticospinal or extrapyramidal signs are often present, and the illness may be complicated by focal or generalized seizures. Overall mortality is around 35 percent, with one-third of survivors suffering significant neurologic impairment.

In recent years, small numbers of cases of encephalitis in the United States have been associated with viruses more commonly found in tropical or other countries. The alphavirus, Chickungunya, and the flavivirus, dengue virus, although usually associated with systemic illnesses may rarely cause encephalitis. Chickungunya virus has been associated with both transverse myelitis and myositis. Zika virus, first isolated in Africa, was subsequently detected in outbreaks of infection in Africa, Asia, and the Pacific Islands. An association between Zika virus infection and Guillain–Barré syndrome was noted in French Polynesia in 2013–2014. In that same outbreak it was recognized that the virus is capable of maternal–fetal transmission. Unlike other arboviruses, Zika virus can persist in semen and produce sexually transmitted infection. In 2015–2016, a major epidemic of Zika virus infection in Brazil was followed by a sharp rise in cases of microcephaly and other CNS neurologic abnormalities in newborns as well as clusters of Guillain–Barré syndrome. In the majority (50 to 80%) of patients, Zika virus infection is asymptomatic, and in a minority of patients can cause a systemic illness with rash, low-grade fever, arthralgia, myalgia, and conjunctivitis. The major neurologic complications of Zika virus infection are Guillain–Barré syndrome and, less commonly, encephalitis or encephalomyelitis. A major concern with Zika virus—unlike other related agents—is that inapparent or mild infection in pregnant women can result in devastating fetal neurologic injury.

Two additional groups of arthropod-borne infections occur outside the United States and should be considered when evaluating patients with encephalitis coming from endemic areas (Table 42-1). Tick-borne encephalitides relate to multiple viral agents existing throughout Eurasia, with greatest prevalence in northern Europe and Asia. Japanese encephalitis virus, endemic in eastern and southeastern Asia, results in 15,000 deaths annually. Both tick-borne encephalitis and Japanese encephalitis may present with findings similar to those produced by WNV, including flaccid paralysis.

Rabies Virus

Rabies virus is an unenveloped single-stranded RNA virus that is a member of the Lyssavirus genus of the family Rhabdoviridae. Rabies virus exists worldwide. In developed countries where canine rabies vaccination is mandatory, predominant animal reservoirs include bats, skunks, foxes, and raccoons. In the United States, most—but not all—human cases result from bat bites. In less developed countries, dogs are the source of most human cases; other animals including infected monkeys, sometimes kept as pets, may account for a minority of cases.[10]

Rabies virus is typically acquired through the bite of an infected animal; rare cases have occurred following exposure to aerosolized rabies virus or after inadvertent transplantation of infected tissue. The virus may remain latent at the site of an infected bite for 6 or more years before the onset of neurologic disease. Unlike most other viruses causing encephalitis, rabies is specifically neurotropic: the virus enters peripheral nerve fibers at the site of inoculation, is carried proximally by reverse axoplasmic flow, and progressively infects the CNS through neuron-to-neuron spread (the centripetal phase of infection). The virus then spreads outward within nerves (the centrifugal phase of infection) to involve multiple tissues including salivary glands, corneas, and the heart. In animals, this centrifugal phase of infection, with shedding of salivary virus, may occur prior to clinical disease.[10]

Rabies classically begins with dysesthesias at the site of the bite, followed by progressive neurologic involvement with a clinical picture (termed "furious rabies") of agitated delirium, stimulus-sensitive laryngeal spasm with hydrophobia, prolonged inspiratory spasm, and progression to coma and death. Rabies may also present as a more classic encephalitis with stupor and coma ("dumb rabies"), or as an ascending paralysis, similar to Guillain–Barré syndrome, followed by signs of CNS involvement. Rabies should be considered in appropriate clinical settings, in particular when there is a history of animal bite or of recent or remote travel to, or residence in countries where rabies is a significant health problem. There may be no history of a bite, however. The minute punctures caused by bat bites may go unnoticed, or, alternatively, the animal bite may have occurred long enough ago to have been forgotten. MRI may show ill-defined, mild T2-hyperintensities in the brainstem and hippocampus; early in the disease these lesions may fail to enhance with gadolinium. Specific diagnosis of rabies is made by identifying rabies antigen in nuchal biopsy or by PCR from saliva or CSF.[10]

Management of rabies consists of two strategies: prevention of clinical disease by immunotherapy and immunization at the time of the bite and supportive treatment of clinical rabies. Preventive therapy involves washing the area of the bite thoroughly, infiltrating the area with rabies virus-specific immunoglobulin, and administration of diploid cell rabies vaccine. This treatment, when administered soon after the bite, is highly effective in preventing clinical rabies. Once clinical rabies develops, the patient's course may be influenced by a wide variety of CNS, autonomic, and systemic complications. Rabies is almost invariably fatal; fewer than 10 patients are known to have survived, and of these, only one made a full recovery. Of interest, a handful of patients known to have received infected corneal tissue or organs failed to develop clinical rabies. One patient surviving rabies was treated with midozalam and ketamine, but the use of these agents in other cases has been unsuccessful.

Other Viruses

Although enteroviruses are most commonly associated with viral meningitis, they may also cause encephalitis and rarely may result in paralytic disease. Enterovirus 71, a cause of hand, foot, and mouth disease and herpangina in children, may cause encephalitis with involvement of the brainstem or, less frequently, the cortex, cerebellum, or spinal ventral roots. In some patients, MRI abnormalities are detected on diffusion-weighted (DWI) or FLAIR sequences. Beginning in 2014, an upsurge of cases of paralytic illness, now known as acute flaccid myelitis, was noted in children nationwide. This illness is characterized by the acute development of flaccid limb weakness accompanied by spinal cord gray matter lesions on MRI and electrodiagnostic evidence of motor neuron injury.[11] Although a minority of patients may exhibit clinical improvement in weakness, most patients have poor recovery. Although other agents have been reported in this condition, epidemiologic evidence supports an association with enterovirus D68.[11]

The mouse arenavirus LCMV usually causes meningitis but may occasionally cause encephalitis. Infection in children and adults is rarely fatal, but clinical recovery and return of CSF to normal can be prolonged. LCMV meningoencephalitis is one of the few viral CNS infections that may cause hypoglycorrhachia. Parvovirus B19, the agent of the childhood condition erythema infectiosum (fifth disease), is an uncommon cause of encephalitis in both children and adults. Human herpesviruses type 6 (HHV-6, associated with roseola infantum) and type 7 (HHV-7) have been associated with seizures or, rarely, encephalopathy in early childhood. In one study, HHV-6 was detected in the CSF of 40 percent of patients with encephalitis of otherwise undetermined cause. Important viruses to consider in patients exposed in Southeast Asia include Japanese encephalitis virus and the bat henipavirus, Nipah virus (Thailand) (Table 42-1).

Epstein–Barr virus (EBV), the agent of infectious mononucleosis, has been associated with a wide variety of infectious and postinfectious neurologic disorders in both immunologically normal and immunocompromised patients. The association of EBV with specific disease presentations, however, is made difficult by two properties of the virus. First, EBV infects and can remain latent in B lymphocytes for many years. For this reason, PCR amplification of EBV DNA from CSF in patients with suspected CNS infection may simply indicate the presence of the virus in lymphocytes rather than proving it as a causative agent. Second, like HSV, EBV can reactivate under situations of physiologic stress, so that a rise in antibody titer in the setting of acute illness may or may not be indicative of disease causation.

Viral Encephalitis in Immunocompromised Patients

Impairment of host B- or T-cell response, whether because of congenital immunodeficiency, HIV infection, or iatrogenic immunosuppression, may result in infection with unusual agents or produce atypical infection by more common viruses. Because control of enteroviral infection depends heavily on antibody, enteroviruses have been associated with chronic meningitis and progressive encephalitis in children with X-linked hypogammaglobulinemia or X-linked hyper-IgM syndrome; these patients exhibit ongoing presence of enteroviral RNA in CSF and may show continued enterovirus excretion in stool. Chronic enteroviral meningoencephalitis has also been reported in patients treated with the anti-CD20 monoclonal agent rituximab. Impairment of T-cell immune response, as in HIV-infected or immunosuppressed patients, may lead to infection with less commonly pathogenic agents such as JCV, cytomegalovirus, adenovirus, HHV-6, or HHV-7, or may result in prolonged or atypical presentations of infections with HSV or VZV. HSV and VZV are treatable with acyclovir, as is the case in immunologically intact patients. Treatment of cytomegalovirus CNS infections has usually involved ganciclovir, foscarnet, or a combination of both agents; cidofovir has been used as a second choice (Table 42-4). Cases of encephalitis associated with HHV-6 have been treated with ganciclovir, foscarnet, or a combination of the two drugs. CNS infections in immunocompromised patients may involve common infections as well as those caused by unusual organisms. An important point to remember in dealing with CNS infections in severely immunocompromised individuals—especially those infected with HIV—is that more than one infective agent may be present.

Progressive Multifocal Leukoencephalopathy

PML is an uncommon opportunistic infection of immunocompromised patients. Its causative agent, the human polyomavirus JCV, affects over 50 percent of individuals worldwide by late adult life[12]. Acute viral infection is not known to cause symptomatic illness, but the virus establishes protracted infection of renal tubular epithelial cells and other tissues, possibly including the brain. In PML, JCV produces lytic infection of oligodendrocytes, causing areas of demyelination; astrocytes are also infected in some cases. PML was initially described as a rare disorder of patients with hematologic malignancies and in immunosuppressed patients. In untreated acquired immunodeficiency syndrome (AIDS), however, 4 percent of patients will die of PML, and PML can be the presenting illness in patients with HIV. In recent years, PML has also become increasingly frequent in patients treated with the more aggressive immunosuppressive regimens now used for collagen-vascular diseases and solid organ or hematopoietic stem cell transplantation. PML has also become a significant—although infrequent—complication of treatment with natalizumab and, to a lesser degree, other monoclonal immunosuppressive agents such as rituximab, efalizumab, alemtuzumab, brentuximab vedotin, and TNF-α inhibitors.[12] The course of PML involves the progressive development of multifocal neurologic deficits which may involve motor control, sensation, speech, vision, or cognition. Occasional patients develop cerebellar or brainstem signs, but clinical involvement of the spinal cord is virtually never present. Rarely AIDS patients have been reported to develop JCV infection of cerebellar granule or other neurons. PML is presumptively diagnosed by MRI, which typically shows multifocal white matter lesions in the cerebrum or, less often, brainstem or cerebellum (Fig. 42-4)[12]; PML lesions are often not apparent on CT. Although PML lesions usually do not enhance, gadolinium enhancement may occur in AIDS and in patients in whom PML is a consequence of treatment with natalizumab or other monoclonal agents. A definitive diagnosis of PML is made by PCR amplification of JCV DNA from the CSF. Sensitivity of PCR in early studies approached 80 to 90 percent. However, in HIV patients treated with antiretroviral therapy, PCR is positive in only around 60 percent of cases.

There is no proven treatment for PML.[12] Cytosine arabinoside has been reported to have limited efficacy in non-AIDS patients only. Cidofovir, mefloquine, and mirtazapine have not been effective in controlled trials. Some recent reports of success with immune checkpoint inhibitors need to be confirmed in larger trials. Restoration of host immune function with antiretroviral therapy in AIDS patients may lead to stabilization or improvement, as may reduction of immunosuppressive therapy in transplant recipients or other patients receiving these drugs. Treatment of PML in cases

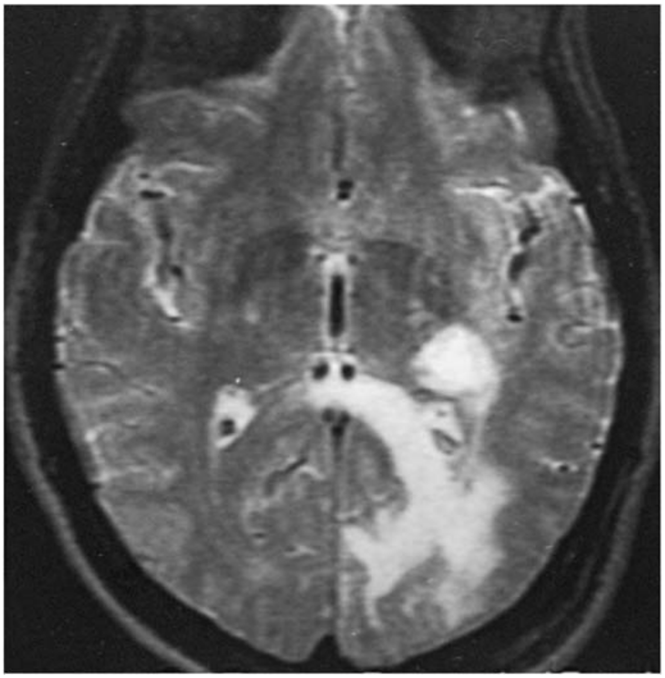

FIGURE 42-4 ■ Progressive multifocal leukoencephalopathy: axial T2-weighted MRI showing multifocal involvement of cerebral white matter.

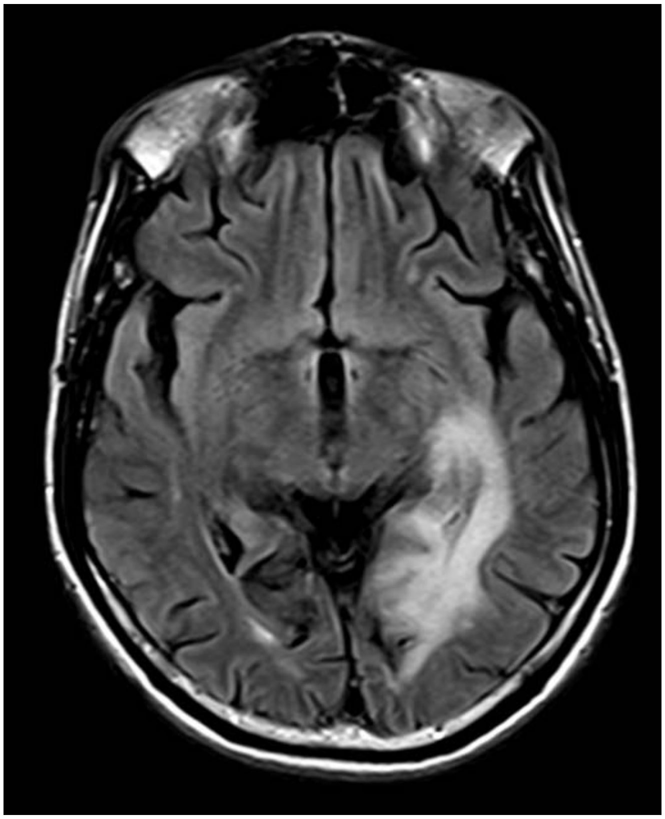

FIGURE 42-5 ■ FLAIR MRI showing PML with immune reconstitution inflammatory syndrome (IRIS) in a patient with human immunodeficiency virus (HIV) following institution of antiretroviral therapy. There is edema in and surrounding a lesion within the left posterior cerebral white matter.

associated with natalizumab or similar agents involves withdrawal of that agent and plasma exchange or immunoabsorption to remove the agent from the circulation; this approach has been used frequently with natalizumab-associated PML but much less frequently in cases of PML associated with other monoclonal agents. Improvement of immune status may cause a fulminant immune reconstitution inflammatory syndrome (Fig. 42-5).

Approach to Patients With Viral Encephalitis

Viral encephalitis should be suspected in any patient presenting with signs suggesting acute involvement of the brain parenchyma, especially in individuals with fever and alteration of consciousness. Meningeal signs may or may not be present. Signs indicating temporal lobe involvement suggest herpes simplex encephalitis, but other viral encephalitides may have a similar presentation as may occasional bacterial infections or autoimmune encephalitis from antineuronal antibodies. Patients often have an elevated peripheral white blood cell count, but signs of systemic infection may also be absent. Diagnosis relies heavily on clinical findings, MRI, and the results of CSF analysis. MRI in herpes simplex encephalitis characteristically shows abnormalities of one or both temporal lobes, at times with involvement of the orbitofrontal cortex, insula, or cingulate gyrus. Similar findings, however, may be seen in other potentially treatable conditions including neurosyphilis and autoimmune encephalitis. The CSF in viral encephalitis typically shows significant pleocytosis and an elevated protein but normal glucose concentration. The pleocytosis is commonly lymphocytic, but is neutrophilic in rare cases. A depressed CSF glucose level, while not typical, has been described in VZV, LCMV, mumps, and HSV-2 infections. CSF should be sent for PCR for HSV, and consideration should be given to ordering PCR for other agents. Film array PCR, which tests for multiple infectious agents, may provide rapid diagnosis but should be supplemented with conventional PCR. Detection of virus-specific IgM in CSF is more sensitive than PCR for the diagnosis of WNV and may be useful in other arboviral infections where PCR is negative. Similarly, elevated CSF titers of IgG may be more sensitive than PCR in encephalitis due to reactivated VZV. Lumbar puncture may need to be deferred when there is evidence on examination, CT, or MRI of increased intracranial pressure or mass lesion.

Acyclovir should be initiated presumptively where viral encephalitis is strongly suspected and should be continued until PCR has been shown to be negative for HSV (Table 42-4). Because the initial PCR in herpes simplex encephalitis may occasionally be falsely negative, acyclovir should be continued in seriously ill patients until a second CSF PCR, obtained 3 to 7 days later, is also negative. Acyclovir should also be continued if VZV is detected by CSF PCR or serology. Ganciclovir should be instituted if CMV or HHV-6 infection is diagnosed; ganciclovir may be supplemented with foscarnet (Table 42-4). Antibacterials should be initiated if bacterial meningitis, brain abscess, or parameningeal infection is suspected.

Treatment of encephalitis is otherwise supportive. Seizures may require intravenous fosphenytoin, levetiracetam, or other agents. Cerebral edema is a major concern in severe encephalitis; dexamethasone (10 mg orally or intravenously followed by 4 mg every 6 hours), mannitol, and hyperventilation have all been used in individual cases, but their efficacy is unproven. Decompressive craniectomy has resulted in patient survival with good initial outcome in a few cases of herpes simplex encephalitis complicated by fulminant cerebral edema. Cerebral salt wasting or SIADH may require treatment with hydration and sodium supplementation, or fluid restriction, respectively. Attention must be given to preventing complications of severe illness such as pneumonia, deep venous thrombosis, and decubitus ulcers. Recovery in viral encephalitis may be extremely prolonged, with the full extent of recovery not realized for many months.

PRION DISEASES

Prion diseases represent a group of rare disorders including Creutzfeldt–Jakob disease (CJD), new variant CJD (vCJD), Gerstmann–Straussler–Schenker disease, familial fatal insomnia, kuru, and variably protease-sensitive prionopathy. Prion diseases of animals include scrapie of sheep (the prototype for this group of conditions), bovine spongiform encephalopathy (BSE), wasting disease of deer and elk, and transmissible mink encephalopathy. Prion diseases are not caused by viruses but rather by a self-replicating isoform of a normal intracellular sialoglycoprotein. The normal cellular protein is termed “PrP(c)” and the self-replicating protein causing disease is referred to as “PrP(Sc).” PrP(Sc) does not contain nucleic acid, its presence does not elicit an immune response, and it is not inactivated by many agents normally used for decontamination. Interaction of PrP(Sc) with PrP(c) appears to be essential for disease. Except in familial cases, PrP(Sc) is thought to arise from a spontaneous mutation in PrP(c). Several different subtypes of CJD have been associated with homozygosity or heterozygosity of methionine or valine at codon 129 of the *PrP* gene, differences in variation in glycosylation patterns of PrP(Sc), and patterns of electrophoretic mobility of PrP(Sc) after proteinase K digestion. Prion diseases have repeatedly been shown to be transmissible through PrP(Sc)-contaminated material, including PrP(Sc)-containing human grafts of dura mater or other tissues, contaminated electrodes used for intracerebral recording, and human pituitary-derived growth hormone. In the case of vCJD, transmission has occurred predominantly through ingestion of contaminated beef, but it has also occurred through blood transfusion.

The most common human prion disease is CJD, which occurs worldwide with 1 to 2 cases per million population per year. The average age at onset is 60 years, with an equal sex distribution. Most cases are sporadic (sCJD), but 12 percent cluster in families. The condition affects the CNS only, without systemic symptoms. The onset of CJD is typically with subtle changes in cognition and personality changes that may include apathy, irritability, depression, or paranoia. Occasional patients present with ataxia, spasticity, or visual complaints. These initial symptoms are followed by progressive dementia, often involving parietal lobe symptoms and, at times, aphasia. As the disease progresses, over 85 percent of patients develop stimulus-sensitive myoclonic jerks that tend to disappear as the disease progresses to profound dementia and a vegetative state. CJD is untreatable, and its course is relentlessly progressive, resulting in death within 6 months to 2 years.

The diagnosis of CJD has traditionally been made on the basis of clinical presentation, EEG, MRI, and evaluation of CSF for the proteins 14-3-3, tau, and neuron-specific enolase. The yield of these studies, however, varies among the different subtypes of CJD. CSF cell count and protein levels are usually normal, such that significant pleocytosis suggests strongly that the diagnosis is incorrect. The EEG initially may show only mild slowing but subsequently becomes strikingly abnormal, with repetitive, periodic, stereotyped, bilaterally synchronous sharp waves that usually occur at a frequency of 1 to 2 per second and are often associated with myoclonic jerks. This periodic EEG activity may give way to generalized slowing late in the disease. MRI has become the most useful initial diagnostic test in suspected CJD and typically shows foci of increased signal in the putamen, caudate, thalamus, and gray matter of the cerebral cortex. These findings are most prominent on DWI sequences and, with less sensitivity, FLAIR sequences (Fig. 42-6); MRI changes are not reliably present in familial CJD. Detection of 14-3-3 and tau proteins as well as neuron-specific enolase in CSF provides supportive evidence for the presence of CJD in patients with clinical, EEG, or MRI markers of the disease. None of these CSF markers is specific for CJD, however, and their use in unselected patients may lead to erroneous diagnosis. Recently, a sophisticated molecular technique, the real-time quaking-induced conversion test (RT-QuIC) has come into use, based on the self-replicating (self-seeding) nature of PrPSc.[13] This test, now in its second generation, allows rapid diagnosis of CJD and other prion diseases from CSF with a specificity of 98.5 to 100 percent and a sensitivity of 92 to 95 percent.[13] Postmortem diagnosis can be made by the characteristic brain histopathology and staining with specific prion antibodies or by demonstration of prions from homogenized brain using immunodiagnostic procedures or the RT-QuIC assay.

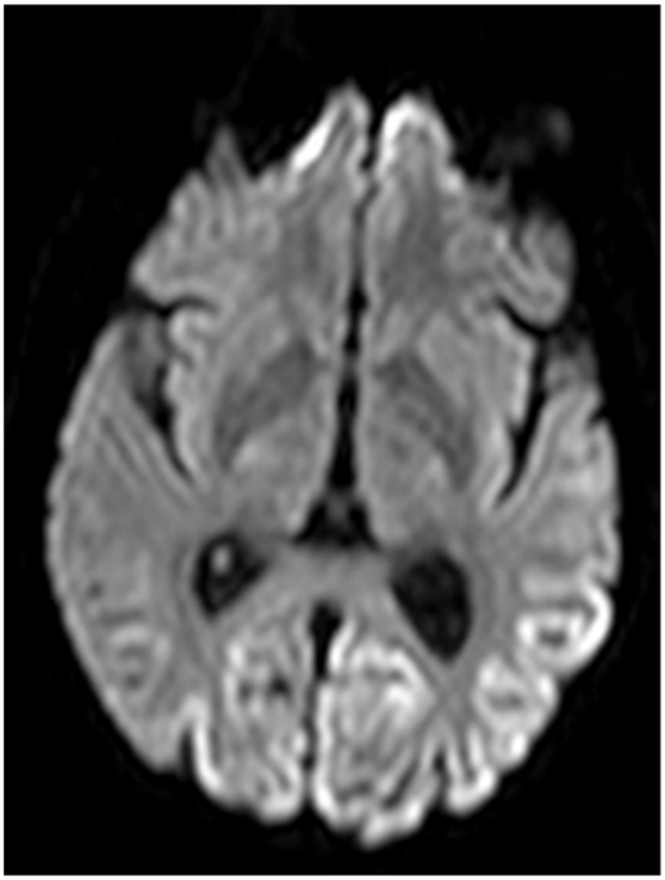

FIGURE 42-6 ■ Creutzfeldt–Jakob disease. Diffusion-weighted MRI image showing restricted diffusion within the cortical ribbon of the posterior hemispheres bilaterally.

In general, animal prion diseases such as scrapie have not been thought transmissible to humans. However, the appearance in Britain of BSE ("mad cow disease"), a prion disease, was followed by an outbreak of human cases of vCJD, which were presumably acquired by ingestion of contaminated beef. Human cases peaked in the year 2000 after extensive culling of affected cattle. Cases of vCJD have occurred primarily in younger individuals and have tended to present with psychiatric signs, with dementia and painful sensory symptoms occurring commonly. In contrast to the general population, all patients studied with vCJD have been homozygous for methionine at codon 129 of the *PrP* gene. Unlike sporadic CJD, the EEG in vCJD only rarely shows periodic activity. MRI typically demonstrates increased signal in the pulvinar on DWI and FLAIR sequences. Survival in vCJD may be more prolonged compared with sCJD. Unlike sCJD, there have been cases of vCJD transmitted by blood transfusion.

SARS-CoV-2

COVID-19 infection, caused by the SARS-CoV-2 virus, has numerous neurologic manifestations that more commonly occur in patients with more severe respiratory presentations requiring hospitalization. CNS involvement includes an incidence of ischemic stroke that is higher than with other similar severe respiratory viral illnesses, such as seasonal influenza. Mechanisms underlying ischemic stroke are likely varied and include systemic hypercoagulability and viral involvement of the heart leading to a central embolic source. An encephalopathy is also common, resembling hospital-acquired delirium. Headache is a well-described heralding feature of the illness. Brain autopsy series suggest that direct viral involvement of the brain, a SARS-CoV-2 viral encephalitis, is rare, and likely most CNS symptoms are reflective of the effects of systemic illness including a massive cytokine response in those who are severely affected.

Peripheral nervous system manifestations include myalgias and an elevated serum creatine kinase, which is common among those with moderate-to-severe respiratory involvement. Guillain–Barré syndrome, likely postinfectious in nature, has been described in small series. Loss of smell is common, even in individuals with mild disease, and in some cases does not rapidly recover with illness resolution. This anosmia is probably due to involvement of the olfactory epithelium, although MRI evidence of hyperintensity in the olfactory nerve and brain regions responsible for olfactory processing has been described.

Postinfectious autoimmune encephalitis and myelitis can occasionally occur following COVID-19 infection. Treatment is uncertain, but intravenous immunoglobulin (IVIg) and plasmapheresis have been tried alone or in combination. Long-term neurologic effects following resolution of the illness remain unknown. Some patients have described a more long-term mild cognitive syndrome that merits further investigation.

POSTINFECTIOUS COMPLICATIONS OF CENTRAL NERVOUS SYSTEM VIRAL INFECTION

The interaction of an infective agent with the host immune system usually results in containment of the agent and eradication of disease. In some instances, however, systemic or CNS viral infections may induce an immune response that reacts not only with the infecting agent but also with components of nervous tissue. Neurologic injury with antineuronal autoantibodies is seen in anti-NMDAR (or, rarely $GABA_AR$) encephalitis which may follow herpes simplex virus encephalitis. In addition, autoimmune CNS injury can occur follow systemic infection and may result in postinfectious encephalomyelitis, acute hemorrhagic leukoencephalitis, transverse myelitis, or injury to the peripheral nervous system resulting in peripheral nerve involvement including plexopathy and the Guillain–Barré syndrome (see Chapter 60). Rarely, optic neuritis may also occur as a postinfectious condition.

Autoimmune Encephalitis Following Herpes Simplex Encephalitis

In roughly 25 percent of cases, individuals surviving herpes simplex encephalitis may develop an apparent clinical relapse caused by anti-NMDAR antibodies; the illness may begin between 7 days and 2 months following infection.[7] Affected children below the age of 4 tend to develop choreoathetosis and may develop refractory seizures. Affected adults exhibit behavioral changes without choreoathetosis; seizures in adults are uncommon. The diagnosis is made by detection of anti-NMDAR antibodies in CSF or (of less sensitivity) serum. In rare cases, antibodies have been detected to a second neuronal membrane protein, the $GABA_A$ receptor.[7]

Postinfectious Encephalomyelitis

Postinfectious encephalomyelitis is defined as an acute, monophasic demyelinating illness occurring within 2 to 4 weeks of a viral or other infection (Table 42-5).[4,14] The condition bears strong similarity to two other conditions: postvaccination encephalomyelitis, which follows immunization, and the experimental autoimmune demyelinating disease, experimental allergic encephalomyelitis. Postinfectious encephalomyelitis and postvaccination encephalomyelitis have been grouped under the common term *acute disseminated encephalomyelitis* (ADEM), which is a final common pathway of autoimmune CNS injury that may be produced by a variety of infectious agents or immunizations.

Postinfectious encephalomyelitis is more common in children than in adults and is rare in the elderly. In children, the peak age of onset is 5 to 8 years. The onset of postinfectious encephalomyelitis may be preceded by fever, malaise, headache, nausea, vomiting, or combinations of these symptoms. These prodromal symptoms are followed by the abrupt—at times fulminant—onset of CNS dysfunction. Altered mental state is almost universal and may range from drowsiness to frank coma. Meningeal signs are common. Neurologic examination may reveal unilateral or bilateral corticospinal tract signs, hemiplegia, ataxia, aphasia, sensory loss, visual field defects, or cranial nerve palsies. Focal or generalized seizures occur in up to 70 percent of children under 5 years of age, 80 percent of whom may develop status epilepticus. Occasionally, postinfectious encephalomyelitis may be accompanied by optic neuritis or by involvement of the peripheral nervous system. The simultaneous occurrence of central and peripheral demyelinating events appears to be more common in adults than children. A syndrome of ataxia may be seen in patients following chicken pox or, less frequently, other viral infections.

The presence of multifocal neurologic signs should raise the level of suspicion of ADEM, as should the presence of signs referable to both the CNS and the peripheral nervous system. Excluding active nervous system infection is important. CSF typically shows a lymphocytic pleocytosis; however, roughly 30 percent of patients will have a mixed pleocytosis with neutrophilic predominance. Traditionally, the presence of oligoclonal bands was considered unusual; however, oligoclonal bands have now been detected in 20 percent of patients with ADEM. In more recent studies, oligoclonal bands were reported in nearly two-thirds of individuals presenting with illnesses initially diagnosed as ADEM, but over half of these patients are subsequently diagnosed as having multiple sclerosis.

MRI with gadolinium enhancement is the diagnostic study of choice in ADEM. T2 and FLAIR sequences classically show multiple, large, asymmetric, irregularly shaped lesions involving the subcortical white matter and the gray–white junction of both cerebral hemispheres (Fig. 42-7). The periventricular white matter may be involved, but lesions confined to the corpus callosum are unusual, in contrast to multiple sclerosis. Gadolinium enhancement is seen in 30 to 100 percent of patients and may vary with stage of the disease. Ring-enhancing lesions are sometimes present. However, the presence of ring-enhancing lesions should raise the possibility of brain abscess or other active CNS infection. Spinal cord involvement, usually with extensive edema and swelling, may occur in children or adults and has a predilection for the thoracic region. The majority of these lesions will resolve over time.

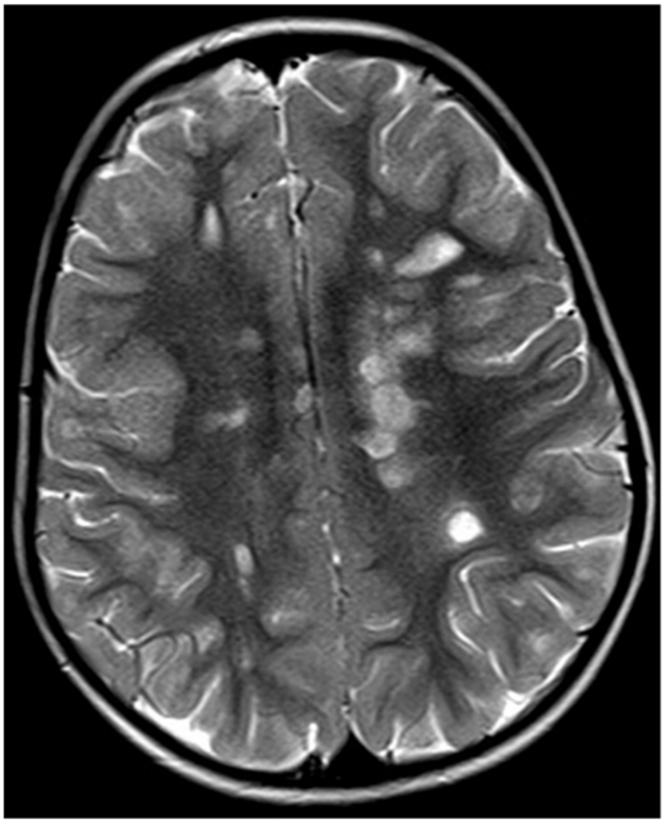

FIGURE 42-7 ■ Acute disseminated encephalomyelitis. T2-weighted MRI showing multifocal areas of increased signal in the white matter. (From Wender M: Acute disseminated encephalomyelitis (ADEM). J Neuroimmunol 231:92, 2011, with permission from Elsevier.)

Acute Hemorrhagic Leukoencephalitis

In roughly 2 percent of children (more rarely in adults), postinfectious encephalitis may present with fulminant hemorrhagic demyelination and cerebral edema, a condition termed "acute hemorrhagic leukoencephalitis," "acute necrotizing hemorrhagic leukoencephalitis," or "Weston Hurst syndrome." MRI demonstrates not only demyelination but also hemorrhage, edema, and at times evidence of ischemia on DWI MRI. In contrast to postinfectious encephalomyelitis, mortality is greater than 50 percent.

Transverse Myelitis

Postinfectious encephalomyelitis may be confined to the spinal cord, resulting in transverse myelitis (Table 42-5). Unlike postinfectious encephalomyelitis, which is more frequent in young children, transverse myelitis is more common in the second decade of life. In the majority of cases, the condition involves the thoracic level of the spinal cord.[15] Onset of symptoms is often abrupt, with rapid progression to maximal deficit; in some patients, however, progression occurs over 1 to 2 weeks. Symptoms typically include fever, back and leg pain, muscle weakness, sensory disturbances, and sphincter dysfunction. Neurologic examination may demonstrate corticospinal tract signs and level-specific sensory loss. The patient may initially exhibit flaccid weakness that progresses over weeks to spasticity. CSF usually shows a lymphocytic or polymorphonuclear pleocytosis with protein levels that may be as high as 500 mg/dL. MRI of the spinal cord often demonstrates focal areas of increased T2 signal. Acute transverse myelitis may represent the first episode of multiple sclerosis, neuromyelitis optica spectrum disorder, or antimyelin oligodendrocyte glycoprotein antibody-related encephalomyelitis. MRI may have diagnostic value in differentiating these entities from postviral transverse myelitis, and partial transverse lesions are more likely to represent these relapsing demyelinating conditions.

TABLE 42-5 ■ Major Viruses Associated With Postinfectious Neurologic Complications

Postinfectious Encephalomyelitis	Transverse Myelitis	Cerebellar Ataxia	Guillain–Barré Syndrome
Varicella-zoster virus	Measles virus	Varicella-zoster virus	Measles virus
Measles virus	Mumps virus	Measles virus	Epstein–Barr virus
Mumps virus	Varicella-zoster virus	Epstein–Barr virus	Cytomegalovirus
Rubella virus	Rubella virus	Influenza virus	Influenza virus
Influenza virus	Influenza virus		Varicella-zoster virus
Enteroviruses	Epstein–Barr virus		HIV
Coronaviruses	Enteroviruses		Dengue virus
HIV	HIV		
HTLV-1	HTLV-1		
Hepatitis A, B, C, E	Hepatitis A, B, C		
Herpes simplex virus	Herpes simplex virus		
Epstein–Barr virus	Human herpesvirus 6		
Cytomegalovirus	Hantavirus		
Human herpesvirus 6	Dengue virus		
Hantavirus (puumala virus)			
Dengue virus			
Smallpox (historic)			

HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus.

Approach to Patients With Postinfectious Neurologic Injury

Patients with clinical relapse following herpes simplex virus encephalitis should be retested for the virus using CSF PCR but should also be tested for anti-NMDAR antibodies in both serum and CSF. Treatment, while awaiting results, should include both acyclovir and high-dose methylprednisolone. Once the presence of viral DNA has been excluded in CSF, acyclovir can be stopped. Methylprednisolone may be supplemented by treatment using plasma exchange, IVIg, or plasma exchange followed by IVIg. The initial approach to the patient with suspected Guillain–Barré syndrome involves hospitalization and, if the patient is demonstrating respiratory failure, intubation (see Chapter 60). The major initial step in patients with suspected postinfectious encephalomyelitis is to exclude multifocal CNS infection or, less likely, vasculitis. In patients with transverse myelitis, extrinsic spinal cord compression requiring surgery must be excluded. Lumbar puncture is of diagnostic value in Guillain–Barré syndrome. In contrast, the most valuable diagnostic test in postinfectious encephalomyelitis or transverse myelitis is contrast-enhanced MRI using gradient echo or susceptibility-weighted images to detect blood products indicative of acute hemorrhagic leukoencephalitis. In Guillain–Barré syndrome, the efficacy of plasma exchange and IVIg has been demonstrated in controlled trials, as discussed in Chapter 60. In contrast, the treatment of ADEM is typically based on case reports and observational studies; some evidence exists for the use of methylprednisolone, usually given at a dose of 1 g daily for 5 days. Plasma exchange (usually five exchanges in total, performed daily or every other day) and IVIg, given as a total dose of 2 g/kg over 3 to 5 days, have also been used, either in combination with methylprednisolone or after methylprednisolone failure. A variety of other immunosuppressive agents including cyclophosphamide have been used in individual cases. Initial treatment of acute transverse myelitis typically involves high-dose intravenous methylprednisolone. Although treatment of acute hemorrhagic leukoencephalitis is frequently unsuccessful, occasional patients have survived after early treatment with combinations of methylprednisolone, IVIg, plasma exchange, or cyclophosphamide[4].

ACKNOWLEDGMENTS

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CHAPTER

43

HIV and Other Retroviral Infections of the Nervous System

MICHAEL J. PELUSO ■ SERENA SPUDICH

HIV BEYOND THE IMMUNE SYSTEM
HIV IN THE NERVOUS SYSTEM
NEUROLOGIC DYSFUNCTION IN THE SETTING OF ANTIRETROVIRAL THERAPY
  HIV-Associated Neurocognitive Disorder
    Asymptomatic Neurocognitive Impairment
    Mild Neurocognitive Disorder
    HIV-Associated Dementia
    Etiology
    Diagnosis and Management
    Treatment
  Targeted Treatment of CNS HIV Infection
  Progressive Disease Despite Systemic Response
    Cerebrospinal Fluid Escape Syndromes
    CD8$^+$ T-Cell Encephalitis
  Emerging Issues in Neurologic HIV Infection
    HIV and Hepatitis C Coinfection
    Aging With HIV Infection
    Stroke
  Central Neurotoxicity of Antiretroviral Agents
NEUROLOGIC DYSFUNCTION IN ANTIRETROVIRAL-NAÏVE PATIENTS
  Effects of Primary HIV in the Central Nervous System
  CNS Complications of Longstanding Untreated HIV Infection
    Classic HIV-Associated Dementia
    Opportunistic Infections
SPINAL CORD DISEASE ASSOCIATED WITH HIV INFECTION
HIV-ASSOCIATED PERIPHERAL NEUROPATHIES
  Distal Sensory Polyneuropathy
  Inflammatory Polyneuropathies
MUSCLE DISORDERS AND HIV INFECTION
INFECTION WITH HUMAN T-LYMPHOCYTIC VIRUS TYPE I
  Pathogenesis of Neurologic Disorder
  Symptoms, Signs, and Course of Infection
  Diagnostic Studies
  Treatment

Human immunodeficiency virus type 1 (HIV-1) infection involves the central nervous system (CNS) beginning during primary viremia and continuing over the course of untreated infection.[1] Although the majority of patients with HIV infection do not present with neurologic symptoms, HIV disease has protean manifestations in the CNS determined largely by host characteristics such as immune status, treatment history, and access and adherence to antiretroviral therapy (ART).

HIV BEYOND THE IMMUNE SYSTEM

Nearly four decades after the report of five unexplained cases of *Pneumocystis carinii* pneumonia in men suffering from what would eventually become recognized as the acquired immunodeficiency syndrome (AIDS), HIV infection remains the subject of intense biochemical, molecular, clinical, and epidemiologic investigation. HIV infection is a bloodborne and sexually transmitted disease that impacts both individuals and public health and has disproportionately affected vulnerable and marginalized populations including the poor and underserved, injection drug users, commercial sex workers, and men who have sex with men. The epidemic has also changed in the last decades. What once was largely a disease of young men who have sex with men in urban centers has expanded to affect all populations; the highest route of overall transmission of HIV is currently through heterosexual contact, often in rural areas, underserved and marginalized populations, and individuals unaware of their risk of HIV acquisition.

It is estimated that there are currently 38 million people living with HIV worldwide and 1.7 million new infections annually. Around one million individuals die

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from the disease and its sequelae each year. Although the greatest number of new infections and the worst outcomes occur in the lowest-resource settings in sub-Saharan Africa and Southeast Asia, nearly 40,000 individuals are newly infected in the United States each year.

A better understanding of the virus's characteristics, including its pathogenesis and transmission patterns, has led to both prophylactic and therapeutic interventions, but many questions about the pathogenesis of HIV infection remain unanswered. An increased focus on the effects of HIV infection beyond the immune system has emerged, including its end-organ effects on the nervous system.

HIV IN THE NERVOUS SYSTEM

HIV is a single-stranded, positive-sense retrovirus of the genus *Lentivirus*. Once transmitted to a new host, the virus uses a reverse transcriptase to transcribe viral RNA into DNA. This DNA is, in turn, integrated into the genome of the host. The stages of HIV infection are divided into the acute phase that immediately follows transmission and includes the $CD4^+$ T-cell nadir; the asymptomatic latent phase characterized by a slow decline in $CD4^+$ T cells; and the symptomatic phase of chronic AIDS. In antiretroviral-naïve patients, it takes approximately 10 years to develop AIDS, although this time may be extended indefinitely with combination ART (Fig. 43-1). Following the development of AIDS, median survival is typically between 1 and 4 years.

It is increasingly recognized that the body's reaction to HIV infection can be as damaging as the activity of the virus itself, and this is particularly true in the nervous system. The inflammatory milieu that is induced by the activity of HIV in invading cells and that triggers an immune response has important implications throughout the time course of infection. It is thought that HIV pathogenesis within the CNS is mediated primarily by inflammation induced by both systemic immune activation as well as HIV infection of macrophages, microglia, and astrocytes. It is hypothesized that an indirect toxic injury to neurons results from a cascade of chronic and persistent neuroinflammation, in part fostered by cytokines produced by infected or activated cells within the

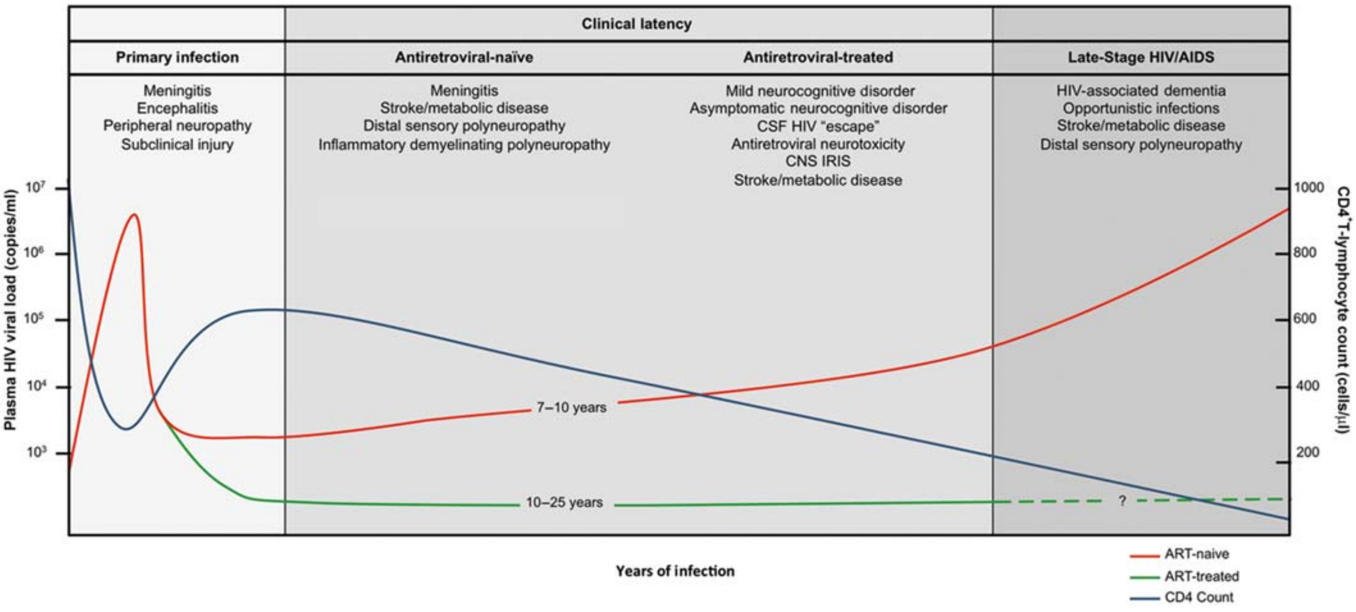

FIGURE 43-1 ■ Typical time course of HIV-1 infection and characteristic neurologic abnormalities. Primary HIV infection refers to the first year following viral transmission, which includes the acute retroviral syndrome, widespread distribution of the virus, the seeding of lymphoid organs, and the $CD4^+$ T-cell nadir. After a recovery in the $CD4^+$ T-cell count, infected individuals enter a long period of clinical latency in which they experience a slow decline in the $CD4^+$ T-cell population. If treatment is not initiated, the $CD4^+$ T-cell count falls to critically low levels and the patient develops acquired immunodeficiency syndrome (AIDS) after 7 to 10 years. This period is characterized by viral proliferation, acquisition of opportunistic infections, and end-organ damage in a variety of body systems, ultimately leading to death from one or a combination of these causes. If treatment is initiated, clinical latency persists for an undetermined period of time, but patients continue to be at risk of a variety of neurologic complications, including several unique to individuals on therapy.

brain. In the earliest stages of infection, the virus crosses the blood–brain barrier for the first time and initiates cytokine release that contributes to breakdown of that barrier. Other effects include a cerebrospinal fluid (CSF) pleocytosis, macrophage and lymphocyte activation, interference with neuronal synthesis and maintenance pathways, and ultimately neuronal injury that can be detected through biomarkers and neuroimaging. Although control of the virus through the initiation of ART can decrease the viral load and suppress the immune response, the CNS remains particularly vulnerable to further insult and may not normalize as well as systemic compartments.[2]

Recent studies of the end-organ effects of HIV beyond the immune system have led to the recognition of a biologic compartmentalization that allows for infection and injury of target tissue, independent evolution of the virus from its counterparts in the plasma, and protection of the virus from systemic therapy. The existence of these distinct biologic compartments, such as those in the breast and genital tract, facilitates viral replication, complicates viral eradication, and leads to organ-specific effects. Chronic HIV infection is associated with the establishment of a CNS reservoir of infection, as evidenced by the detection of HIV DNA in perivascular brain macrophages, microglial cells, and astrocytes, compartmentalization of HIV quasi-species in CNS tissues, and clinical cases of isolated CNS "escape" from ART.[3] Targeting treatments and strategies toward CNS reservoirs of HIV has become an important aspect of recent efforts to achieve a cure for HIV infection.

NEUROLOGIC DYSFUNCTION IN THE SETTING OF ANTIRETROVIRAL THERAPY

The introduction of ART in the mid-1990s fundamentally altered the landscape of both systemic and neurologic HIV disease. The profound immunodeficiency associated with HIV/AIDS that acted as the substrate for the "classic" neurologic manifestations of the disease itself and the opportunistic infections with which it was associated can now be significantly delayed or prevented, transforming the disease from one that was uniformly fatal into a manageable chronic illness.

In general, ART suppresses both plasma and CSF viral levels and improves neurologic outcomes in patients with HIV infection.[4] Typically, plasma HIV RNA suppression is paralleled by suppression in the CSF, and the initiation of ART also limits the extent of immune activation in the CSF, as measured by white blood cell count and immunologic markers. With systemic control of the virus and improved immune status has come a striking decline in the occurrence of neurologic opportunistic infections over the last three decades, while the attenuation of viral replication and immune activation in the CNS has resulted in a decline in the incidence of the most dramatic forms of HIV-associated neurologic disease. Nevertheless, even individuals with well-controlled HIV infection continue to experience neurologic dysfunction which, although often less pronounced than the illnesses experienced 40 years ago, has the potential to seriously impact productivity and quality of life.

HIV-Associated Neurocognitive Disorder

What was previously defined in its most severe form as the AIDS–dementia complex is now represented by a spectrum of disorders reflecting the variability in presentation, outcome, and impact of neurologic disease.

HIV-associated neurocognitive disorder (HAND) comprises a diverse set of neurocognitive diseases, ranging from clinically asymptomatic impairment to severe dementia.[5] HAND is a clinical diagnosis defined by abnormalities identified through neuropsychologic testing and is subdivided into three categories of increasing severity: asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia (HAD) (Table 43-1).[5] These diagnoses require the administration of a specific neuropsychologic test battery assessing language, attention, executive functioning, memory (learning and recall), processing speed, visuospatial abilities, and motor skills. While the incidence of the most severe manifestations of HAND has decreased in the setting of widespread access to ART, mild-to-moderate HAND has persisted and has become the most prevalent primary CNS complication of HIV infection.

ASYMPTOMATIC NEUROCOGNITIVE IMPAIRMENT

The most benign and most common manifestation of HAND is asymptomatic neurocognitive impairment, which has been identified in approximately one-third of people living with HIV. It is characterized as a subclinical cognitive decline with decreased performance on neuropsychologic testing in two or more domains not attributable to comorbid conditions (e.g., mood disorders, substance abuse). It specifically requires that

TABLE 43-1 ■ Classification of HIV-Associated Neurocognitive Disorder (HAND) in Patients Being Treated With Antiretroviral Therapy

	Asymptomatic Neurocognitive Impairment (ANI)	Mild Neurocognitive Disorder (MND)	HIV-Associated Dementia (HAD)
Neuropsychologic Testing Abnormalities	One standard deviation below the age- and education-adjusted mean on two cognitive domains	One standard deviation below the age- and education-adjusted mean on two cognitive domains	Two standard deviations below the age- and education-adjusted mean on two cognitive domains, especially learning, information processing, and attention/concentration
Effect on Everyday Function	None	Mild May be noted by self or others, including impairments in mental acuity, work efficiency, maintenance of home life, and social functioning	Marked May be noted by self or others, manifesting as severe difficulty in work, independent maintenance of home life, and social functioning
Dementia	Absent	Absent	Present Other causes such as opportunistic infection, vascular dementia, severe active drug use must be absent

no negative impact on everyday functioning is present, distinguishing it from mild neurocognitive disorder.

It is unclear whether asymptomatic neurocognitive impairment predicts more severe neurologic impairment later in the course of HIV, whether it contributes to neuropathologic vulnerability, and whether initiation of ART before clinically evident neurocognitive impairment develops might prevent ongoing deterioration.

MILD NEUROCOGNITIVE DISORDER

A form of mild cognitive impairment is being recognized increasingly in individuals treated with ART, who typically have a relatively reconstituted immune system characterized by high CD4$^+$ T-cell counts and suppressed or undetectable viral loads. As the population of patients with chronic, well-controlled HIV infection continues to grow, so too does the overall prevalence of mild neurocognitive disorder, which approaches 12 percent in some studies.

The diagnosis of mild neurocognitive disorder depends on the detection of abnormalities in neuropsychologic testing in attention, processing speed, memory, and executive function domains. In contrast to those with asymptomatic neurocognitive impairment, patients typically are aware of a subtle impairment in cognitive ability and increased difficulty carrying out activities of daily living. Mild neurocognitive disorder can also affect both pyramidal and extrapyramidal motor systems, producing symptoms such as ataxia, tremor, and incoordination that may worsen over time. It can lead to behavioral symptoms that are independent of those associated with mood disorders concomitant with HIV infection.

HIV-ASSOCIATED DEMENTIA

The disorder initially described 25 years ago as the AIDS—dementia complex is now known as HAD, the most dramatic manifestation of HAND. The diagnosis remains a challenge, as there are no diagnostic studies or laboratory tests that are specific for HAD.

The diagnosis of HAD is based on progressive neurocognitive impairment and the exclusion of other conditions that can mimic these symptoms including CNS opportunistic infections and mass lesions such as tumors. HAD is still identified most commonly in patients not taking ART; the prevalence in treated patients may be as low as 2 percent. HAD most typically occurs in patients with slowed cognitive processing in the context of longstanding HIV infection and is often accompanied by motor abnormalities such as slowed movement and spastic gait along with hyperactive muscle stretch reflexes. Evaluation with computed tomography (CT) or magnetic resonance imaging (MRI) of the brain is used to exclude other AIDS-related neurologic conditions, including opportunistic infections and CNS lymphoma. With these diagnoses excluded, diffuse cerebral atrophy and subcortical or periventricular white matter changes are consistent with, although not specific for, HAD.

ETIOLOGY

Although the biologic substrate of HAND in the setting of ART is unknown, one potential mechanism involves injury occurring in the earliest stages of HIV infection. Such injury would begin before treatment is initiated and would continue along a trajectory that may or may not be mitigated by initiation of ART. After several

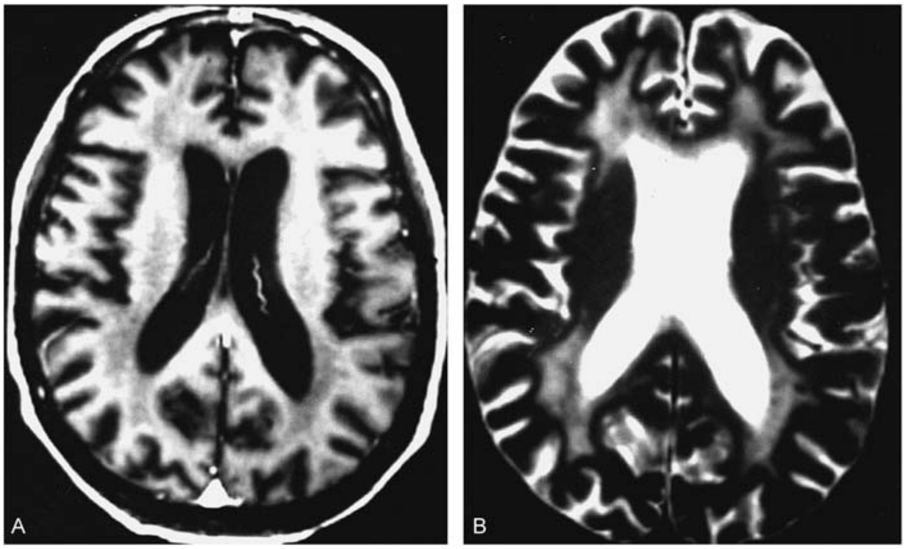

FIGURE 43-2 ■ *A*, T1-weighted magnetic resonance image (MRI) of patient with HIV-associated dementia showing marked cerebral and cortical atrophy. *B*, T2-weighted MRI of the same patient showing extensive hyperintense signal abnormalities in the white matter. (From Berger JR: AIDS and the nervous system. p. 851. In Aminoff MJ (ed): Neurology and General Medicine. 4th Ed. Churchill Livingstone Elsevier, Philadelphia, 2008, with permission.)

years, a combination of host susceptibility and disease factors may result in the development of symptomatic neurologic disease.

Another possibility is that, due to the compartment-specific nature of CNS HIV infection, neurologic injury is incurred despite the initiation and continuation of systemically suppressive treatment. Even in individuals with no overt signs or symptoms of neurocognitive impairment, the presence of HIV in the CNS may result in constant low-level inflammation and immune activation that may lead to ongoing brain injury. CSF immune activation, brain inflammation detected by magnetic resonance spectroscopy, and microglial activation persist in patients taking long-term suppressive ART.

DIAGNOSIS AND MANAGEMENT

Because HAND has no specific diagnostic markers, it is necessary to exclude CNS opportunistic infections, delirium, toxic-metabolic disorders, psychiatric disease, and other neurodegenerative conditions before making the diagnosis. Although traditional neuroimaging is useful in excluding other HIV-associated disease processes, including CNS lymphoma, infections, and inflammatory processes, there are no findings on standard imaging that are specific for HAND (Fig. 43-2). Efforts to use more advanced neuroimaging techniques to identify mild HAND have included brain mapping, high-field structural imaging, functional MRI, and magnetic resonance spectroscopy. The utility of these new modalities remains to be determined. Fig. 43-3 provides an algorithm for the identification and management of HAND.[6]

Performance on neuropsychologic tests in severe forms of HAND improves with the initiation of ART. The introduction of ART has been associated with a decreased incidence and prevalence of HAD despite increases in the prevalence of milder forms of HAND. While initiation of ART significantly improves cognitive performance and neurologic function in antiretroviral-naïve patients with HAD, this improvement is frequently incomplete. Furthermore, many patients already taking ART also have HAND.

TREATMENT

Adjunctive therapies that target the CNS have been studied in an attempt to attenuate the inflammatory events that are postulated in the pathogenesis of HAND. Adjunctive therapies other than antiretroviral agents, including memantine, selegiline, and nimodipine, have not been successful. Valproic acid and lithium have been hypothesized to decrease HIV replication and neuroinflammation through their glycogen synthase kinase-3β activity, as have serotonin reuptake inhibitors such as citalopram and paroxetine through an unknown mechanism; no clear improvement in HAND has been demonstrated with these agents. Due to its anti-inflammatory and antiviral effects, the antibiotic minocycline has also been suggested as a potential therapy, but randomized trials have been unsuccessful. Statins, which decrease progression of vascular disease in people living with HIV and have widespread

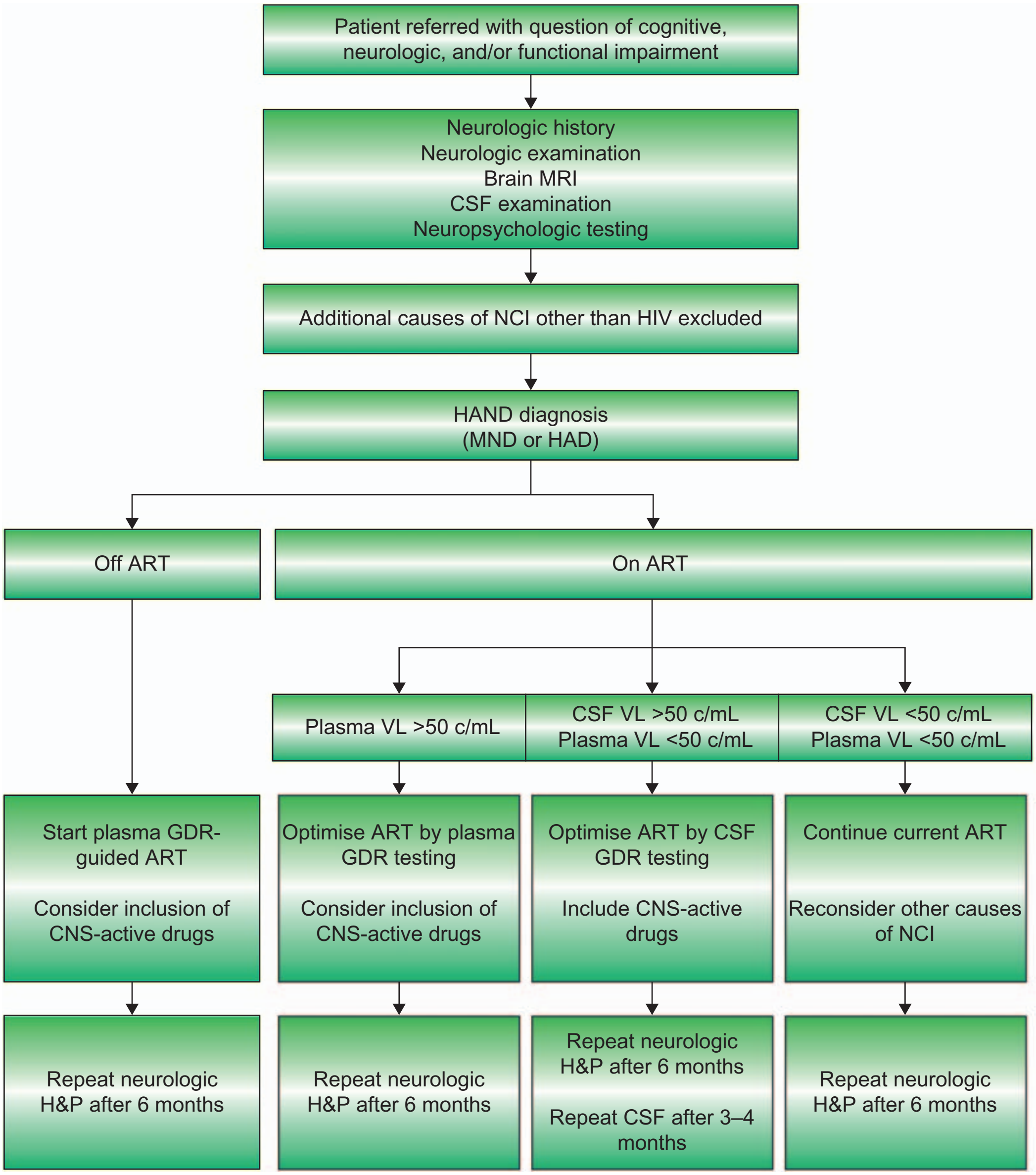
Patient referred with question of cognitive, neurologic, and/or functional impairment
Neurologic history
Neurologic examination
Brain MRI
CSF examination
Neuropsychologic testing
Additional causes of NCI other than HIV excluded
HAND diagnosis (MND or HAD)
Off ART
On ART
Plasma VL >50 c/mL
CSF VL >50 c/mL Plasma VL <50 c/mL
CSF VL <50 c/mL Plasma VL <50 c/mL
Start plasma GDR-guided ART
Consider inclusion of CNS-active drugs
Optimise ART by plasma GDR testing
Consider inclusion of CNS-active drugs
Optimise ART by CSF GDR testing
Include CNS-active drugs
Continue current ART
Reconsider other causes of NCI
Repeat neurologic H&P after 6 months
Repeat neurologic H&P after 6 months
Repeat neurologic H&P after 6 months
Repeat CSF after 3–4 months
Repeat neurologic H&P after 6 months

FIGURE 43-3 ■ Diagnostic and management algorithm for HIV-associated neurocognitive disorder. GDR, genotype drug resistance; H&P, history and physical examination; MND, mild neurocognitive disorder; NCI, neurocognitive impairment; VL, viral load. (Adapted from the European AIDS Clinical Society Guidelines, Version 6.1, November 2012.)

anti-inflammatory effects, are under study. Methylphenidate successfully treats fatigue and psychomotor slowing in patients with HAND, but does not alter the course of the disease. An alternate treatment strategy using antiretroviral drugs that penetrate into the CNS is discussed later.

Targeted Treatment of CNS HIV Infection

By separating the CNS from the systemic circulation, the blood–brain and blood–CSF barriers affect the ability of antiretroviral agents to access the CNS compartment. In addition, local spontaneous replication of HIV within this viral sanctuary may allow for independent mutations of HIV virions. While the response of CSF HIV RNA levels to ART parallels that in the plasma, the rate of decay in the CSF may be more gradual in some patients, suggesting a compartmentalization characterized by slower cell turnover, extended macrophage release, or attenuated drug entry.

Because of the blood–brain barrier, HIV in the CNS may be protected from the full effect of antiretroviral agents, especially those drugs that are large or hydrophilic. The CNS penetration-effectiveness (CPE) index represents an effort to estimate quantitatively the relative ability of each antiretroviral agent to penetrate the

TABLE 43-2 ■ Proposed CNS Penetration-Effectiveness (CPE) Ranks for Commonly Used Antiretroviral Agents

	CNS Penetration-Effectiveness Score			
Drug Class	**4**	**3**	**2**	**1**
NRT inhibitor	Zidovudine	Abacavir Emtricitabine	Lamivudine Stavudine	Didanosine Tenofovir Zalcitabine
NNRT inhibitor	Nevirapine	Delavirdine Efavirenz	Etravirine	—
Protease inhibitor	Indinavir/r	Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r
Entry inhibitor	Vicriviroc	Maraviroc	—	Enfurvirtide
Integrase inhibitor	—	Raltegravir	—	—

Adapted from Clifford DB: HIV and the Brain: Update 2010. International AIDS Society—USA, March 22, 2010, New York, NY.
Higher numbers indicate higher CNS penetration and effectiveness. NRT, nucleoside reverse transcriptase; NNRT, non-nucleoside reverse transcriptase; /r, ritonavir boosted.
Note: Data on integrase inhibitors are not currently available.

CNS and interfere with CSF HIV replication. Each agent is assigned a CPE score based on presumed CNS exposure and efficacy of the drug in relation to others in its class (Table 43-2).

Some studies have shown that antiretroviral regimens with higher CPE scores tend to be more successful at achieving HIV RNA suppression in the CNS. While more potent HIV RNA suppression in this compartment might be expected to lead to better neurocognitive outcomes, results have been mixed, with some studies showing that regimens with higher CPE scores actually lead to poorer neurocognitive performance or only benefit those patients treated with more than the standard ART regimen of three drugs.

The inability of ART to control the potential reservoir of HIV that exists in monocytes or other myeloid lineage cells has been proposed as one possible explanation for continued neurocognitive impairment in the setting of ART. As a result, a monocyte efficacy (ME) score has been proposed as an alternative means of quantifying the ability of antiretroviral agents to affect neurologic outcomes. Preliminary work has suggested that the ME score correlates with neurocognitive performance even when the CPE score does not.

Progressive Disease Despite Systemic Response

Several new clinical syndromes have been recognized in patients taking systemically suppressive ART, often after a long period of apparently successful treatment.

CEREBROSPINAL FLUID ESCAPE SYNDROMES

CSF escape is a phenomenon of CSF/plasma discordance. In an individual with suppressed plasma HIV RNA, CSF escape occurs when the CSF HIV RNA is detectable despite plasma HIV suppression.[3] In an individual with detectable plasma HIV RNA, CSF escape occurs when the level of HIV RNA in the CSF exceeds that in the plasma. A subset of individuals with CSF escape become symptomatic. Patients with symptomatic CSF escape include a broad spectrum of individuals with ART-managed HIV, including those persistently suppressed or well-controlled for many years, as well as those with recent spikes in viral load and those beginning to achieve viral control.

The pathogenesis of symptomatic CSF escape is related to the failure of ART to suppress local CNS infection despite peripheral CD4$^+$ T-cell reconstitution. Although detectable CSF HIV RNA in the context of ART is required, it is not sufficient, since asymptomatic CSF escape has been identified as a frequent finding (up to 18%) in asymptomatic individuals undergoing lumbar puncture in the context of HIV research studies. A moderately reconstituted immune system may actually contribute to the symptomatic syndrome by eliciting a symptomatic inflammatory response and providing a substrate for ongoing discordant HIV replication within the CNS. This process may lie on the spectrum of the immune reconstitution inflammatory syndrome (IRIS), but may represent a stable state of antigen and immune response within the CNS, rather than the exaggerated response upon immune reconstitution that occurs in IRIS. Low $CD4^+$ T-cell nadir (i.e., <250 cells/mm^3) may be a risk factor for CSF "escape," suggesting that a history of advanced immunosuppression may confer increased risk of the syndrome. In addition to resistance and poor penetration, poor medication adherence might also contribute by leading to insufficient drug concentrations in the CSF and thus to the selection of resistant virus within this compartment.

The clinical features of symptomatic CSF escape include a variety of subacute to acute progressive neurologic symptoms including cognitive, sensory, and motor impairment resulting in substantial disability. The diagnosis is achieved through the recognition of plasma/CSF discordance and the exclusion of opportunistic infections including progressive multifocal leukoencephalopathy (PML). Imaging may show white matter hyperintensities on T2-weighted MRI sequences; these are often periventricular. Resistance genotyping of CSF HIV may demonstrate mutations in the CSF viral subpopulation. The CSF typically shows elevated protein levels and white blood cell counts consistent with an inflammatory response beyond that which is seen in healthy controls without HIV infection and neurologically asymptomatic subjects with HIV who are taking ART. Elevated CSF neopterin and pronounced inflammation with $CD8^+$ T-lymphocyte infiltration is seen on brain biopsy. Some patients with CSF escape demonstrate improvement when the ART regimen is optimized based upon the results of genotyping and the CPE score of the current ART regimen.

Notably, a secondary CSF escape syndrome can also occur in the setting of a documented non–HIV-related CNS infection or inflammatory condition. It is possible that each type of CSF escape is associated with a different pathophysiologic process.

$CD8^+$ T-CELL ENCEPHALITIS

Reports of a $CD8^+$ T-cell encephalitis in individuals taking ART probably reflect a disorder on a similar spectrum as CSF escape.[7] Individuals often experience memory impairment associated with extrapyramidal symptoms. This disorder has been considered a form of CNS IRIS related to HIV itself although, as in symptomatic CSF escape, many of these patients developed the syndrome while apparently immunologically stable on ART. Several reports have demonstrated perivascular inflammation and leukoencephalopathy following initiation of ART, which is consistent with previous descriptions of IRIS relating to other pathogens. There are some reports of this condition responding well to corticosteroids after other infectious processes have been excluded.

Emerging Issues in Neurologic HIV Infection

A number of new concerns regarding neurologic manifestations of HIV have arisen in the era of widespread access to ART; epidemiologic shifts in HIV disease incidence, prevalence, and course; and demographic changes in individuals living with the virus.

HIV AND HEPATITIS C COINFECTION

HIV and hepatitis C virus (HCV) coinfection occurs in up to 40 percent of individuals, due in many cases to similar routes of transmission. Injection drug users are more likely to be coinfected with both pathogens. Patients coinfected with HIV and HCV have more rapid progression of both diseases and worse overall clinical and survival outcomes.

HCV has been detected both in brain tissue and in CSF of HIV and HCV coinfected patients, and HCV core protein has been demonstrated to induce neuronal injury. Magnetic resonance spectroscopy has detected reduced cerebral *N*-acetylaspartate in these patients, further suggesting neuronal injury. HIV and HCV coinfected individuals may exhibit a higher prevalence of multiple neurologic disorders than patients living with HIV alone, including an elevated risk of seizures.

Some studies have indicated that coinfection with HIV and HCV leads to more severe cognitive effects than infection with HIV alone. Others have suggested that while the overall level of neurocognitive deficits is similar, specific impaired cognitive domains may differ.[8]

There are many confounding factors related to combined HIV and HCV disease including mood disorders, substance abuse, and socioeconomic influences. HCV management with interferon-alpha, itself known to cause cognitive abnormalities in uninfected individuals, may result in improved cognitive profiles in the coinfected population. Further work is needed to characterize the impact of modern curative hepatitis C therapies on the epidemiology of neurocognitive impairment in this population.

AGING WITH HIV INFECTION

With widespread access to ART has come a dramatic increase in life expectancy for people living with HIV infection, with some now living with the disease for over 30 years. HIV-associated cognitive deficits, particularly mild HAND, therefore have the opportunity to evolve over time and become confounded by typical age-associated neurocognitive disorders. At the same time, some individuals are beginning to acquire HIV infection at older ages, perhaps resulting in host factors that are different from those that characterized the initial epidemic. The risk of HAND appears to be higher in individuals with advanced age, although there is a need for studies that more accurately characterize its prevalence. Furthermore, differentiating HAND from neurodegenerative diseases like Alzheimer disease can be challenging.[9]

The normal process of aging involves the development of subtle deficits in neuropsychologic domains that parallel those affected by HAND, including processing speed, memory, and attention. Studies have suggested that age has an effect on cognitive impairment in patients living with HIV and that older age at seroconversion and duration of infection may increase the risk of HAD. At the same time, the trajectory of neurocognitive decline appears to be accelerated in older people living with HIV, likely due to a combination of age-related and HIV-related impairment.

Imaging studies of individuals living with HIV older than 60 years have shown disruptions in structural networks that exceed that expected with normal aging, even in the setting of access to ART. Individuals predisposed to neurodegeneration by the apolipoprotein E4 allele exhibit even worse neural network disruption. Aging patients with HIV infection display a diminished utilization of brain reserve; while patients without HAND are able to compensate for age-related declines in attention through utilization of brain reserve, individuals with HAND may be unable to do so, leading to worsening cognitive decline. These changes are possibly related to a combination of declines in dopaminergic function and glial activation in the setting of neuronal injury.

The consequences of HAND in the aging population are significant and include reduced medication adherence and increased mortality. For this reason, regular screening for neurocognitive impairment is crucial. Because of the potentially additive effects of age-related and HIV-associated neurocognitive diseases, older persons living with HIV may require additional medical and social services to optimize outcomes.

STROKE

Stroke is under-reported in people living with HIV; during the ART era, rates of hospitalization for ischemic stroke in patients with HIV have increased dramatically, whereas those in uninfected persons have declined.[10] In the context of HIV infection, ischemic stroke affects patients who are more likely female, younger, and lack traditional risk factors for cerebrovascular disease. HIV infection is an important risk factor for stroke in the developing world as well.

In the pre-ART era, most cases of stroke in people living with HIV were attributed to the intracranial opportunistic infections and tumors associated with advanced immunosuppression. In the ART era, the pathogenesis of stroke in people living with HIV is likely due to a multifactorial combination of HIV infection itself and side effects from the activity of antiretroviral agents including dyslipidemia.

HIV itself induces endothelial activation, which can lead to ischemic vascular events in the heart and brain. Cardiac disease has been increasingly recognized in people living with HIV, and cardioembolic causes of cerebral ischemia are more common than in the pre-ART era. Especially in the late stages of the disease, patients living with HIV may have diastolic dysfunction and HIV-associated dilated cardiomyopathy, which is identified as the cause of stroke in up to 20 percent of patients. While opportunistic infection-related vasculitis was commonly implicated in ischemic stroke in the pre-ART era, a small-vessel vasculopathy related to the virus itself is increasingly common. Hypercoagulability and intracranial aneurysms occur more frequently in this population than the general population and can also lead to stroke.

Although ART increases life expectancy, it also may allow patients to develop age-related atherosclerotic disease. Longer exposure to the virus itself may exacerbate stroke risk through mechanisms described earlier. In addition, the protease inhibitors used in ART regimens contribute to numerous metabolic abnormalities including lipodystrophy, dyslipidemia, and insulin resistance. While some agents are associated with adverse cardiovascular outcomes in large cohort studies, uncontrolled HIV viremia is almost certainly a greater risk factor for stroke than antiretroviral medications. Patients who interrupt therapy to reduce their overall exposure to antiretroviral drugs demonstrate increased cardiovascular-related morbidity and death.

Metabolic disorders also worsen neurologic performance outside of the context of clinically detectable stroke in patients with HIV infection. Insulin resistance and poor glucose control have been associated with poorer neurocognitive performance. Clinical or subclinical carotid artery disease is also associated with neurocognitive decline, and central obesity contributes to worse neurocognitive performance in people living with HIV.

Central Neurotoxicity of Antiretroviral Agents

The tissue-specific adverse effects of antiretroviral agents outside the nervous system include pancreatitis, lactic acidosis, ototoxicity, and lipodystrophy. In addition to controlling systemic HIV levels, a goal of therapy is to protect the brain from damage related to viral pathogenesis and to eliminate the CNS reservoir of the virus. Although ART that achieves sufficient penetration into the CSF can successfully control CNS viral replication, there has been growing concern that the therapeutic concentrations needed to achieve effective viral suppression are associated with an increased risk of neurotoxic adverse effects.

While several drugs may have neurotoxic potential, many of these medications are used rarely in the era of modern ART. The mechanism of antiretroviral toxicity outside the nervous system may relate to inhibition of mitochondrial DNA production, but it is unclear whether this occurs in the CNS. Neurotoxicity may be related not to cell death, but rather to reversible dendritic changes.

The adverse reactions associated with efavirenz are the most common and include sleep disturbances (e.g., abnormal dreams, nocturnal awakening, and insomnia), mood disorders, impaired concentration, and, in some cases, suicidal ideation.[11] These reactions typically occur in the days following initiation of treatment and are most common during the first 4 weeks; nearly half of all patients will experience some form of reaction, and the effects can persist for months or years. The incidence of these side effects may be related to drug concentration, which demonstrates significant variability between individuals, possibly related to differences in liver metabolism. Although the adverse effects of efavirenz have typically been considered mild, they can also manifest as severe depression, mania, and aggression. Neuropsychiatric effects are the primary reason for efavirenz discontinuation.

In many settings, dolutegravir has replaced efavirenz as first-line ART. A large population-based study in Botswana showed a statistically significant but not substantially increased risk of fetal neural tube defects when this agent is used in early pregnancy; it remains part of first-line therapy (with appropriate counseling) in most treatment guidelines. While this drug is generally well-tolerated in adults, there are emerging data that a subset of patients may experience dizziness or insomnia associated with its use.[12] Mood disorders, including depression and suicidality, have also been reported in a small number of patients with pre-existing comorbid psychiatric conditions. Despite these issues, discontinuation of this agent is very low and it has become a crucial component of HIV regimens worldwide.

NEUROLOGIC DYSFUNCTION IN ANTIRETROVIRAL-NAÏVE PATIENTS

The advent of ART has led to a 10-fold decrease in CNS disease. However, some patients still present with the classic complications of AIDS. This decline of neurologic complications in the developed world has not been paralleled in resource-poor settings internationally, where the diagnosis and management of neurologic disease are complicated by a lack of access to HIV diagnostic and neurologic imaging technology and co-infections with endemic pathogens including malaria and tuberculosis. Even in the era in which guidelines recommend treatment for all people living with HIV, many do not have access to ART and begin treatment late in the disease course.

Effects of Primary HIV in the Central Nervous System

The study of neurologic disease in HIV infection has traditionally focused on chronic and late-stage neurocognitive manifestations, but recent work has shown effects of HIV on the CNS much earlier in the disease course, including during primary HIV infection (defined as the first year following transmission of the virus). Primary HIV infection is characterized by a rapid and dramatic rise of HIV RNA levels in the plasma, accompanied by an increase in HIV antibody levels that are detectable within 2 weeks of transmission by fourth-generation enzyme immunosorbent assay tests. In at least two-thirds of individuals, the period of seroconversion is accompanied by the acute retroviral syndrome, characterized by vague symptoms of fatigue, malaise, fever, and anorexia. Within a few months of seroconversion, a partially effective immune response causes HIV RNA to stabilize at a reduced, chronic, individual-specific level. This plateau is a result of the increased activity of CD8$^+$ T cells in conjunction with a decreased reservoir of $CD4^+$ T cells available for infection by the virus.

In addition to the acute retroviral syndrome, a subgroup of individuals newly infected with HIV develop neurologic symptoms and signs around the time of seroconversion. HIV can be found in the CSF and brain tissue of patients during the earliest stages of infection, in the weeks to months following viral transmission. Indeed, HIV has been identified in the CSF as early as 8 days after transmission.[1] Immune activation accompanies the presence of HIV virions in the CSF during primary infection, and the elevation in CSF leukocyte count, neopterin, and inflammatory cytokines during the first months of infection suggests that CNS injury can take place even during this period. Biomarkers of neuronal injury are elevated in patients with primary HIV infection and correlate with both neuroinflammatory markers and magnetic resonance spectroscopic evidence of neuronal dysfunction.

One of the first syndromes to be linked with primary HIV infection was aseptic meningitis, characterized by a CSF lymphocytosis with or without clinical signs of meningitis. Other individuals experience varying degrees of encephalopathy in the setting of meningoencephalitis, encephalitis, or encephalomyelitis. Acute neuropathies, including facial nerve paralysis and optic neuritis, also occur frequently with seroconversion and are common in acute HIV infection. Although clinically heterogeneous, these neurologic syndromes associated with primary HIV infection share several common features, including onset 2 to 3 weeks after the symptomatic manifestations of the acute retroviral syndrome, a self-limited course, and evidence of temporally associated HIV seroconversion. The pathogenesis of these syndromes is therefore probably due to a host-mediated autoimmune response in the setting of massive systemic immune activation. Evaluation of patients with these acute neurologic syndromes should include not only HIV antibody testing but also nucleic acid testing for the presence of HIV by polymerase chain reaction (PCR) since antibody responses may be absent or indeterminate during the earliest stages of infection.

Symptomatic seroconversion, also characterized by a variety of non-neurologic symptoms, has been associated with more rapid disease progression. It appears that these early signs of neuroinflammation are related to objective neuronal injury, but it is unclear whether inflammation or injury at this early time-point predicts neurologic outcomes in later stages of the disease, and whether the early initiation of ART can ameliorate these processes before systemic immunosuppression occurs.

CNS Complications of Longstanding Untreated HIV Infection

CLASSIC HIV-ASSOCIATED DEMENTIA

The disorder now called HAD was initially described as the AIDS–dementia complex. There are no individual diagnostic studies or laboratory tests that are specific for HAD. Identification of this disorder depends on the recognition of the clinical syndrome and the exclusion of alternative diagnoses. Diagnostic criteria and approach to treatment were described earlier and in Table 43-1. Initiation of ART in these treatment-naïve patients is associated in the majority with a dramatic improvement of clinical signs and symptoms over the early weeks to months of treatment. More gradual improvement may be detectable up to 18 months later.

OPPORTUNISTIC INFECTIONS

For the first two decades following the discovery of HIV infection, opportunistic infections were among the most dramatic and dreaded complications of the disease (Table 43-3).[13] The incidence of these complications has declined with the widespread use of ART in the developed world, but HIV-associated opportunistic infections remain a significant cause of morbidity and mortality worldwide, particularly in individuals whose access or adherence to ART is limited.

Any individual with advanced HIV infection is at risk for the development of a CNS opportunistic infection, including patients with AIDS who are not on therapy, those with undiagnosed HIV (who may initially present with a CNS opportunistic infection), and those in whom ART has begun (who in turn might develop IRIS, as described earlier). More rarely, patients on ART may develop CNS opportunistic infections, due either to failure of complete viral suppression or to lack of immunologic restoration on ART.

CNS opportunistic infections should be considered in patients experiencing significant immunosuppression, typically below 200 $CD4^+$ T cells/μL, although some opportunistic disorders (e.g., tuberculosis meningitis, PML) can manifest in individuals with higher T-cell counts. Diagnosis is typically made using a combination of the clinical presentation (including host factors, symptoms, presence of other known active infections, presence or absence of prophylactic medications, and serologies) combined with CSF and imaging studies. In settings where investigations are limited, clinicians may be required to rely upon the history and physical findings alone.

A description of the time course and determination of whether focal deficits are present are important

TABLE 43-3 ■ Presentation and Diagnosis of HIV-Associated Opportunistic Infections of the Central Nervous System

	Cerebral Toxoplasmosis	**Primary CNS Lymphoma**	**Progressive Multifocal Leukoencephalopathy**	**Cytomegalovirus Encephalitis**	**Cryptococcal Meningitis**	**Tuberculous Meningitis**
Disease Characteristics						
CD4 count	<200	<100	<100	<50	<50	Variable
Time scale	Days	Weeks to months	Weeks to months	Days to weeks	Days to weeks	Days to weeks
Signs/Symptoms						
Alertness	Reduced	Variable	Preserved	Reduced	Variable	Reduced
Fever	+/−	−	−	+/−	+/−	+
Seizures	+	+	−	+	−	−
Headache	+	+	−	−	+	+
Focal deficits	+	+	+	−	−	+/−
CSF Studies						
WBC	Increased	Increased	Unchanged	Increased	Unchanged	Increased
Protein	Increased	Unchanged/increased	Unchanged/increased	Increased	Increased	Increased
Glucose	Decreased	Unchanged	Unchanged	Unchanged	Decreased	Decreased
Other tests	Toxoplasma PCR	Epstein–Barr virus PCR	JC virus PCR	Cytomegalovirus PCR	Increased opening pressure; antigen test	Acid-fast bacilli stain; *M. tuberculosis* PCR
Imaging Findings						
Focal lesions	+	+	+	−	−	−
Number	Multiple	One or few	One or multiple	n/a	n/a	n/a
Mass effect	+	+	−	−	−	−
Enhancement	+(ring)	+(ring or complete)	−	+(periventricular)	+(meningeal)	+(basilar)
Location	Basal ganglia, cortex	Periventricular, subependymal	Subcortical white matter; brainstem	Periventricular	Basal ganglia	Basal ganglia
Special features	Eccentric target sign	Ring- or completely enhancing	Dark on T1, bright on T2	n/a	Gelatinous pseudocysts	Tuberculomas, abscesses

PCR, disease-specific polymerase chain reaction test.

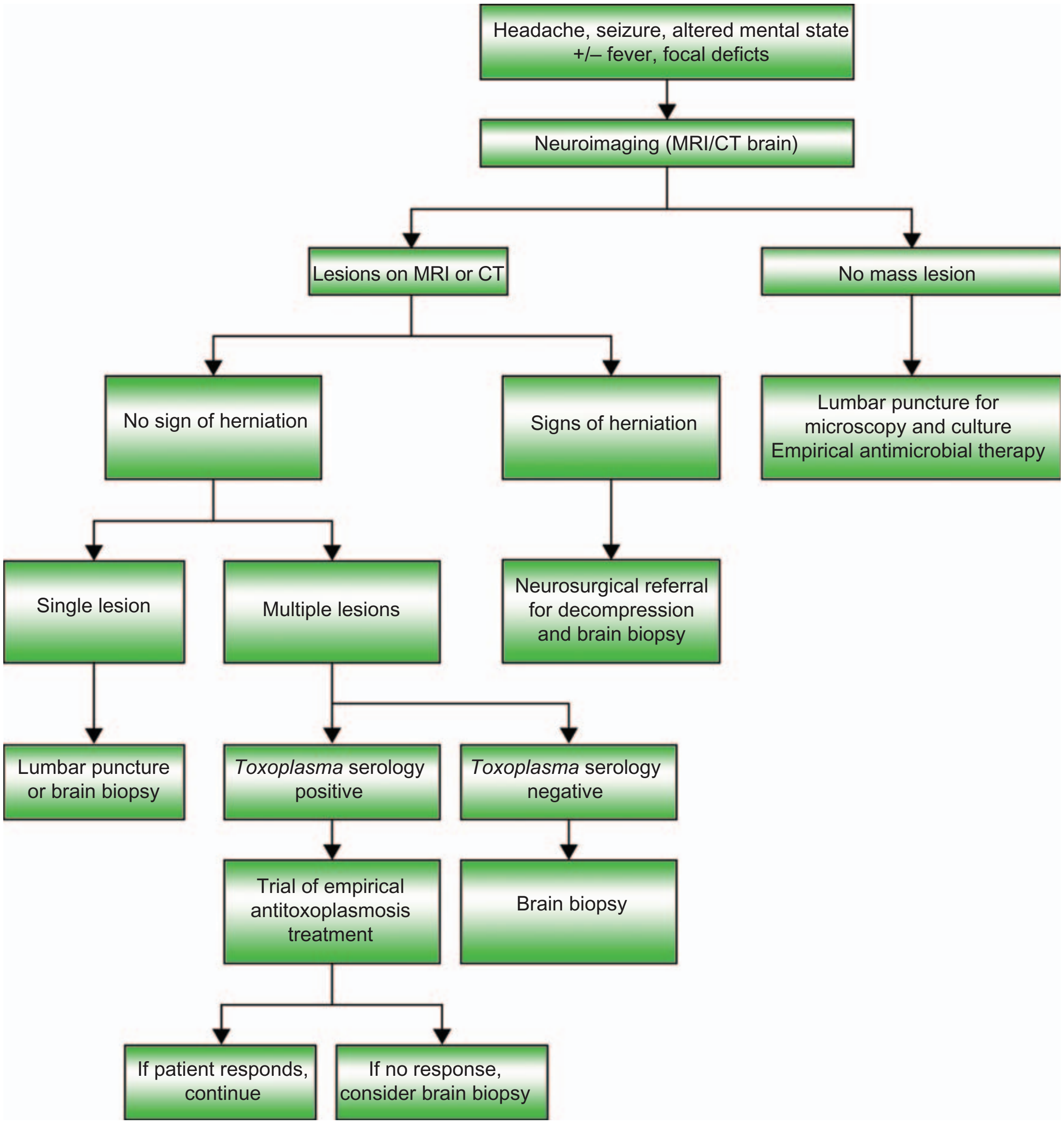
Headache, seizure, altered mental state +/– fever, focal defects
Neuroimaging (MRI/CT brain)
Lesions on MRI or CT
No mass lesion
No sign of herniation
Signs of herniation
Lumbar puncture for microscopy and culture Empirical antimicrobial therapy
Single lesion
Multiple lesions
Neurosurgical referral for decompression and brain biopsy
Lumbar puncture or brain biopsy
Toxoplasma serology positive
Toxoplasma serology negative
Trial of empirical antitoxoplasmosis treatment
Brain biopsy
If patient responds, continue
If no response, consider brain biopsy

FIGURE 43-4 ■ Algorithm of diagnostic principles for CNS opportunistic infections. (Reprinted with permission from Tan IL, Smith BR, von Geldern G, et al: HIV-associated opportunistic infections of the CNS. Lancet Neurol 11:605, 2012.)

elements for determining the identity of a CNS opportunistic infection (Fig. 43-4). Some infections, such as cryptococcal meningitis, cytomegalovirus encephalitis, and toxoplasmosis, manifest acutely over a few days. Others, such as primary CNS lymphoma and PML, follow a subacute course over weeks to months. Focal deficits typically characterize infections that involve mass lesions, such as primary CNS lymphoma or toxoplasmosis, and are also seen in PML. These localizing signs are less frequently present in other opportunistic infections causing meningitis or encephalitis.

Once a particular opportunistic disease process has been identified, ART should be initiated or modified in conjunction with appropriate antimicrobial therapy. Typically such treatment is required until immune recovery ($CD4^+$ T-cell count exceeding 200 cells/μL for 6 months) has been achieved. When this is not possible, patients may need to remain on lifelong antimicrobial suppression.

Multiple opportunistic processes co-exist in up to 15 percent of these patients.[13] The presence of a concurrent process must be considered in patients who worsen despite apparently adequate treatment for the initial infection.

Toxoplasmosis

The incidence of toxoplasmosis encephalitis in people living with HIV has declined substantially since the

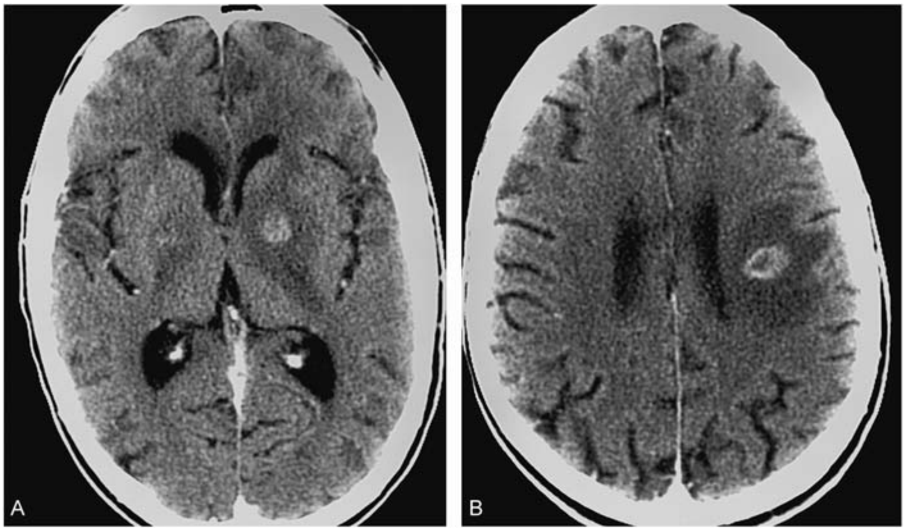

FIGURE 43-5 ■ A 33-year-old HIV-positive man presented with a seizure and right hemiparesis. *A*, Contrast-enhanced CT scan shows edema in the basal ganglia bilaterally, with abnormal central enhancement, more marked on the left than on the right. The ventricles and sulci are excessively prominent for a patient of this age, consistent with the global parenchymal volume loss of HIV dementia. *B*, A more superior image shows a ring-enhancing lesion with surrounding vasogenic edema in the left frontal lobe. The patient's anti-*Toxoplasma* titer was positive, and he responded well to a course of toxoplasmosis-specific therapy, supporting the diagnosis of toxoplasmosis. (Courtesy Nancy Fischbein, MD.)

introduction of ART, but it remains the most common neurologic opportunistic disease associated with HIV infection in many regions. The infection is related to the reactivation of latent toxoplasmic bradyzoites that survive in brain and muscle after the initial ingestion of oocysts and replication of tachyzoites. The immunodeficiency caused by HIV infection results in a loss of the ability of CD4$^+$ T cells to control this latent infection.

Patients with toxoplasmosis present with fever, headache, and focal deficits that may be accompanied by an altered mental state as described in Chapter 46. These symptoms usually present rapidly over a few days to weeks. Brain imaging demonstrates single or multiple ring-enhancing lesions, most often located in the deep gray matter, although they can be present anywhere in the brain (Fig. 43-5). A "target sign" of enhancement has been recently recognized to be a hallmark imaging finding. Serum *Toxoplasma* IgG is typically positive, but, as immunity may wane with advanced immunosuppression, treatment for toxoplasmosis is recommended even in those with negative tests when suspected clinically. CSF PCR-based detection of *Toxoplasma* DNA has a reduced sensitivity in patients with AIDS.

Traditionally, toxoplasmosis has been treated with a combination of pyrimethamine, folinic acid, and sulfadiazine. In resource-poor settings, trimethoprim-sulfamathoxazole has been shown to be equally effective, and this regimen has become increasingly used in the United States due to cost-related access issues for pyrimethamine. Patients typically experience improvement within the first week of initiating therapy, and if there is no response to therapy within 5 days, alternative diagnoses should be considered. After the 6-week induction period, maintenance therapy should continue until the patient's immune system is reconstituted with a CD4$^+$ T-cell count persistently above 200 cells/μL. Compared with other neurologic complications of HIV, there have only been sparse reports of IRIS with toxoplasmosis. In people living with HIV, the 1-year mortality associated with toxoplasmosis is as high as 60 percent, although in patients who have immune recovery due to ART and adherence to antitoxoplasmosis treatment, recovery is possible, sometimes with little or no clinical sequelae of disease.

Primary CNS Lymphoma

Primary CNS lymphoma in HIV patients is most commonly a multicentric, high-grade, B-cell tumor associated with monoclonal Epstein–Barr virus infection. Patients may experience a nonspecific syndrome of lethargy, altered cognition, headache, and focal abnormalities associated with growth of the mass lesion. Symptoms usually are present for several weeks and may be associated with constitutional symptoms such as low-grade fever, weight loss, and night sweats. In some cases, primary CNS lymphoma may present as an infiltrative lesion that resembles an encephalitis or rhombencephalitis, without focal findings or headache.

Classic lesions on MRI are multifocal, supratentorial, and often located along the ependyma. They may demonstrate heterogeneous ring enhancement with contrast, and be accompanied by marked edema and mass effect, leading them to be radiologically indistinguishable from *Toxoplasma* abscesses. More rarely, they may be hypodense on CT or hyperintense on T2-weighted MRI sequences with no enhancement and little mass effect. Patients are often given empiric anti-*Toxoplasma* therapy if radiologically compatible lesions are identified and serum *Toxoplasma* IgG is positive. If no improvement is noted within 5 days, further aggressive evaluation for alternate causes, including primary CNS lymphoma, is warranted. Identification of EBV DNA in the CSF can be a useful test in patients with HIV and suspected CNS lymphoma; although the sensitivity is low, using a cut-off value of 10,000 copies/mL can significantly improve specificity. A positive EBV PCR in CSF combined with a hypermetabolic lesion on positron emission tomography or single-photon emission computed tomography scan has been considered adequate for initiation of treatment for lymphoma. In some cases a brain biopsy is required for definitive diagnosis.

The prognosis of primary CNS lymphoma has improved dramatically in the ART era. Patients are treated with effective ART, combined with antitumor therapy employed for persons who are not living with HIV, including radiation and high-dose methotrexate. However, adverse effects of these intensive life-saving treatments may include neurologic and cognitive dysfunction that can manifest and even progress as patients survive long term into middle and advanced age.

Cryptococcal Meningitis

The inhalation of the encapsulated yeast *Cryptococcus neoformans* from soil or pigeon droppings leads to primary, latent, or disseminated disease (see Chapter 45). Although primary infection is typically pulmonary in nature, cryptococcal meningitis can result from reactivation of latent infection in immunocompromised patients. The reactivated yeast forms cerebral "soap-bubble cysts," which are accumulations in the Virchow–Robin spaces surrounding the deep penetrating vessels.

Cryptococcal meningitis often leads to communicating hydrocephalus. More than 15 percent of patients develop increased intracranial pressure, which may present with headache, vomiting, visual and hearing loss, cranial nerve palsy, altered consciousness, and even death. In some cases, hydrocephalus may be asymptomatic.

The organism may be detected in the CSF with either India ink staining or the more sensitive and specific cryptococcal antigen assays. Cryptococcal serum antigen has been demonstrated to be highly sensitive for CNS disease in people living with HIV. Neuroimaging may be normal or show hydrocephalus, leptomeningeal enhancement, gelatinous pseudocysts (particularly in the basal ganglia), or, more rarely, enhancing lesions in the parenchyma bordering the CSF spaces, especially in the posterior fossa and occipital lobes.

Management of cryptococcal meningitis, particularly when associated with increased intracranial pressure, prevents blindness, deafness, brain injury, and death. Serial daily lumbar punctures, each removing enough CSF volume to keep the pressure below 20 cmH_2O, can improve symptoms and reduce neurologic morbidity. First-line therapy for cryptococcal meningitis is intravenous amphotericin B with oral flucytosine for 2 weeks, followed by oral fluconazole for 8 weeks. Generally, ART should be deferred until at least 4 weeks of antifungal treatment have been provided to minimize the risk of CNS complications and mortality related to IRIS.[14] Prophylaxis with fluconazole should be continued at least until the patient's immune system is reconstituted.

Cytomegalovirus Encephalitis

Cytomegalovirus (CMV) is widespread—most individuals worldwide become infected by adulthood. Encephalitis caused by CMV typically occurs only in patients with advanced immunosuppression ($CD4^+$ count <50 cells/μL). Patients typically appear acutely ill, with a rapidly progressive encephalopathy that may be accompanied by seizures and typically involves bilateral subependymal structures, leading to profound amnesia. In addition, patients may experience visual symptoms including central scotoma, loss of peripheral vision, or floaters—signs of CMV retinitis which, if untreated, can lead to blindness and warrant ophthalmologic evaluation. Additionally, concomitant adrenal involvement can lead to hyponatremia.

The diagnosis of CMV encephalitis involves identifying meningeal or periventricular enhancement on MRI. CSF studies reveal a pleocytosis with neutrophils as the predominant cell type and may also show red blood cells and xanthochromia along with a high protein level. CMV PCR in the CSF is highly sensitive and specific for the diagnosis, and quantitative testing can aid in monitoring the response to therapy.

CMV encephalitis in people living with HIV should be treated with ART plus an anti-CMV agent such as ganciclovir or valganciclovir. Patients are often left with profound morbidity even when the progression of disease is halted. Retinitis can be managed with a sustained-release antiviral intraocular implant and prevented with oral gangciclovir. Other agents, such as foscarnet or cidofovir, can be considered in cases in which leukopenia or resistance is an issue. All patients should continue on prophylaxis with long-term oral therapy until they achieve a persistent $CD4^+$ T-cell count exceeding 200 cells/μL.

Progressive Multifocal Leukoencephalopathy

PML is caused by the JC virus, a common polyomavirus that reactivates in immunosuppressed individuals and occasionally in individuals with high $CD4^+$ T-cell counts. While the sequence of events leading to PML is unclear, it is likely to be related to viral mutations conferring neurovirulence and the subsequent infection of oligodendrocytes and astrocytes.

Patients with PML experience subacute to acute progressive focal neurologic deficits. Brain MRI shows one or more subcortical confluent white matter lesions corresponding to the clinical deficits. These lesions have typical qualities of demyelination, including marked hyperintensity on T2-weighted sequences and hypointensity on T1-weighted sequences, with no mass effect and absent or only trace enhancement with contrast. CSF JC virus PCR is highly specific but has a sensitivity of only 60 to 80 percent in the ART era; repeat CSF analysis may be warranted if the test is negative and clinical suspicion high. A CSF pleocytosis is typically absent and a mildly elevated protein concentration is the most common abnormal finding on routine CSF analysis. Rarely, brain biopsy is required to make the diagnosis.

Immune reconstitution induced by ART results in PML remission in the majority of people living with HIV; before the ART era, remission was rare. Immune reconstitution with ART in patients with PML increases survival from 10 to 75 percent. PML arrests or remits in approximately 50 percent of patients who are being treated with ART.

There is no effective JC virus-directed antiviral therapy despite studies of cidofovir, mefloquine, and mirtazapine. Paradoxically, neurologic IRIS has been extensively described in the context of PML through recognition that the initiation of ART results in emergence of an unexpected number of PML cases, many of which have atypical features on neuroimaging including avid contrast enhancement. These cases of PML suggest that immune reconstitution leads to an extreme, but localized, inflammatory response in a subset of patients, with JC virus serving as the inciting antigen. Corticosteroids may be beneficial in such cases although recommendations are conflicting. Emerging data on approaches using novel immunotherapy, including checkpoint inhibitors, adoptive transfer of donor-derived T-cells, and treatment with interleukin-7, offer hope that more effective treatments are on the horizon.

Tuberculous Meningitis

Nearly one-third of the global population is infected with *Mycobacterium tuberculosis*, a bacillus that is transmitted through aerosolized droplets and controlled by T-cell immunity (see Chapter 40). When this immunity wanes with HIV infection, *M. tuberculosis* disseminates to extrapulmonary sites including the CNS. Within the CNS, granulomas are formed in the subpial and subependymal layers of the brain, and these can expand into abscesses or rupture to cause meningitis. The mortality from tuberculous meningitis in patients with HIV is over 50 percent, and ART initiation does not necessarily improve outcomes.

Despite the importance of rapid treatment of tuberculosis infection, definitive diagnosis is often challenging since the tuberculin skin test and interferon-gamma release assay are particularly insensitive in patients with $CD4^+$ T-cell counts below 200 cells/μL. The CSF profile typically shows increased lymphocytes, depressed glucose, and normal or mildly elevated protein levels. In many resource-poor settings, the diagnosis of tuberculous meningitis may rely only upon CSF studies without a definitive molecular diagnosis through culture or PCR-based techniques.

Management of tuberculous meningitis begins with a standard quadruple-therapy regimen (e.g., rifampin, isoniazid, ethambutol, and pyrazinamide) for 2 months, followed by 9 to 12 months of isoniazid and rifampin maintenance therapy. In cases in which the organism is drug-resistant, second-line therapies including fluoroquinolones and injectable aminoglycosides must be used; worse outcomes occur in these individuals.

Antimycobacterial therapy should begin prior to the initiation of ART in patients with tuberculous meningitis, presumably to decrease the risk of IRIS. Drug–drug interactions between HIV and antituberculous drugs are an important consideration in these cases. The use of adjuvant corticosteroids remains controversial in tuberculous meningitis; studies have suggested that dexamethasone decreases mortality but may not improve morbidity in those patients who survive the illness.

SPINAL CORD DISEASE ASSOCIATED WITH HIV INFECTION

The most common spinal cord disorder in patients with AIDS is vacuolar myelopathy, which before the ART era was present in 30 percent of patients at autopsy and closely associated with opportunistic infections. Patients present with progressive leg weakness and spasticity along with sensory ataxia and loss of vibratory and joint position sense. Urinary frequency and urgency as well as erectile dysfunction may also occur. There is typically an absence of back pain and no involvement of the upper extremities. A lumbar puncture should be performed to exclude infectious or oncologic causes. Spinal MRI should be performed to exclude space-occupying or compressive spinal cord lesions, but is typically normal. In some cases, cord atrophy or nonenhancing T2-weighted hyperintensities may be present, correlating with histopathologic findings of vacuolation.

Management of HIV-associated myelopathy should focus on physical and occupational therapy and symptomatic management, with adjunctive treatments to manage pain, spasticity, and incontinence.

HIV-ASSOCIATED PERIPHERAL NEUROPATHIES

The peripheral nervous system is particularly affected during primary HIV infection, and peripheral neuropathies constitute the most prevalent neurologic problems in patients with AIDS. The most common of these chronic peripheral neuropathies are a distal sensory polyneuropathy and a neuropathy secondary to antiretroviral toxicity.

Distal Sensory Polyneuropathy

Distal sensory polyneuropathy occurs in up to two-thirds of people living with HIV and is most common in older patients with more advanced disease characterized by low $CD4^+$ T-cell counts and high plasma viral loads. It is particularly common in individuals with concomitant alcohol use or diabetes, and in those who have used neurotoxic first-generation antiretrovirals including stavudine and didanosine.

The distal sensory polyneuropathy may be related to loss of distal unmyelinated fibers in addition to Wallerian degeneration of myelinated fibers. Patients experience progressively worsening parasthesias and dysthesias that begin distally and then slowly spread to more proximal regions. In late disease, the thighs and hands may be affected and distal muscle wasting may occur. The diagnosis can usually be made by the history and a neurologic examination, with decreased ankle reflexes and diminished vibratory, pinprick, and temperature thresholds in the legs. Patients with a co-existing myelopathy may have a mixed picture of proximal hyper-reflexia and distal hyporeflexia. Distal sensory polyneuropathy should be considered as a diagnosis of exclusion after other neuropathic processes including diabetes, syphilis, thyroid abnormalities, and vitamin deficiencies are considered. Electromyography and nerve conduction studies demonstrate features of a predominantly axonal neuropathy but are usually not necessary to make the diagnosis.

Treatment begins with the discontinuation or dose reduction of neurotoxic antiretroviral drugs, with subsequent resolution in neuropathic symptoms usually taking between 8 and 16 weeks. Following antiretroviral discontinuation, symptoms might actually worsen for 4 to 8 weeks in a phenomenon known as the "coasting period." Symptomatic management involves treatment of neuropathic pain with gabapentin, pregabalin, lamotrigine, or tricyclic antidepressant medications, which are all generally compatible with antiretroviral medications including protease and integrase inhibitors.

Inflammatory Polyneuropathies

Inflammatory neuropathies are relatively uncommon in patients with HIV infection. Primary HIV infection may be complicated by an acute inflammatory polyneuropathy; patients experience a rapidly ascending paralysis and loss of reflexes. Unlike typical Guillain–Barré syndrome, albuminocytologic dissociation may not occur in the CSF. Chronic inflammatory demyelinating polyneuropathy progresses more slowly and often relapses.

Since inflammatory neuropathies are thought to be associated with an autoimmune component, it has been suggested that they might respond to immunomodulation with plasmapheresis or intravenous immunoglobulin. In severely immunosuppressed patients with evidence of co-existing CMV infection, therapy with ganciclovir, foscarnet, or cidofovir is recommended.

HIV infection may cause a sensory neuronopathy or rarely a systemic vasculitis. The vasculitis typically occurs in the early symptomatic stage of the disease and may lead to a mononeuropathy (single or multiple) or to cranial neuropathies. Nerve biopsy shows a necrotizing vasculitis. Other causes of mononeuropathy, such as herpes zoster, CMV infection, or lymphomatous infiltration of nerve roots, must be excluded. Multifocal neuropathies in people living with HIV may also arise from neurolymphomatosis and diffuse infiltrative lymphocytosis syndrome.

A cauda equina syndrome due to CMV infection may occur with advanced HIV infection or, less commonly, at first presentation. It is characterized by progressive paraparesis and sacral paresthesias, with ascending sensory loss, areflexia, and sphincter dysfunction. A similar presentation may occur in the upper extremities; this polyradiculitis presents with pain, weakness, and often asymmetric atrophy. The CSF typically shows a polymorphonuclear pleocytosis, and CMV may be detected by culture or DNA PCR assay. In occasional instances, cytomegalic cells may be found in the CSF. Treatment is with ganciclovir, foscarnet, or both.

MUSCLE DISORDERS AND HIV INFECTION

These are discussed in Chapter 60 and are mentioned here only briefly. Several muscle disorders may occur in people living with HIV including polymyositis and a syndrome resembling inclusion-body myopathy. A myositis resembling polymyositis also occurs as part of IRIS. Type II muscle fiber atrophy sometimes leads to proximal muscle weakness and wasting, accompanied by a normal serum CK level. Vasculitic processes and opportunistic infections can involve muscle—treatment involves antiretroviral and immunomodulatory agents or specific antimicrobial therapy. Pyomyositis manifesting as localized pain and swelling in a limb is usually associated with *Staphylococcus aureus* infection. Nemaline rod myopathy may occur with or without associated inflammation.

High-dose zidovudine treatment may cause a proximal myopathy associated with myalgias in the thighs and calves. Serum CK levels are normal or mildly elevated. Muscle biopsy reveals "ragged red" fibers consistent with mitochondrial toxicity. Discontinuation of the medication usually results in improvement but recovery is sometimes incomplete.

INFECTION WITH HUMAN T-LYMPHOCYTIC VIRUS TYPE I

Worldwide, as many as 20 million people are infected by the human T-lymphocytic virus type I (HTLV-1), a retrovirus endemic to Japan and equatorial regions of the Caribbean, South America, and Africa. In these areas, the prevalence of HTLV-1 can be as high as 2 percent. In the United States, HTLV-1 infection is most common in Native American and African American populations. Like HIV, HTLV-1 is a bloodborne virus that can be transmitted through sexual contact, breastfeeding, intrauterine infection, intravenous drug use, and exposure to contaminated blood products.

The majority of individuals harboring the HTLV-1 virus are asymptomatic carriers. Between 2 and 3 percent of patients develop adult T-cell leukemia, which in many cases is fatal. Up to 4 percent exhibit a progressive, debilitating myelopathy known as HTLV-associated myelopathy or tropical spastic paraparesis (HAM/TSP).

Although commonly used, the term HAM/TSP is problematic since HTLV-associated disorders are limited neither to myelopathy nor to tropical regions of the world. HAM/TSP is best conceptualized as a variety of neurologic syndromes caused by HTLV-1 infection.

Pathogenesis of Neurologic Disorder

The mechanism by which HTLV-1 induces HAM/TSP is uncertain, but may be related to direct glial cell toxicity, autoimmunity resulting from molecular mimicry, or the generation of myelinotoxic metabolites by a neuroinflammatory response within the CNS. Genetics may also play a role in determining the magnitude of the immune response or in affecting the rate of disease progression.

Symptoms, Signs, and Course of Infection

HAM/TSP presents as a slow, progressive spastic paraparesis accompanied by bladder dysfunction and sensory abnormalities. The most common symptoms are leg weakness and difficulty walking, sometimes associated with leg and back pain and with parasthesias. Falls are common and result in significant morbidity. Urinary symptoms include nocturia and hyperactive bladder; erectile dysfunction also occurs. Patients with HAM/TSP have high rates of co-existing depression.

HAM/TSP is associated with non-neurologic manifestations including pulmonary abnormalities (e.g., centrilobular nodules, thickened bronchovascular bundles, ground-glass opacities, bronchiectasis, intralobular septal thickening), bladder and renal infections, arthritis, and the presence of other autoimmune disorders (e.g., Sjögren syndrome, sarcoidosis). These processes probably result in part from the altered host immune response induced by HTLV-1.

Typical signs in HAM/TSP include a spastic paraparesis with reduced pain sensation, along with bilateral upper-extremity hyper-reflexia in the absence of arm weakness. Urodynamic studies demonstrate bladder dysfunction. Less commonly, patients have neuromuscular manifestations including inflammatory myopathy or demonstrate ophthalmologic findings such as uveitis, retinal vasculitis, or lymphomatous eye infiltration.

Progression from mild to severe disability can range from 2 to 10 years. Risk factors for more rapid progression include severe spasticity, diminished vibration sense, and the presence of tremor. Disease progression is more rapid in women than men, particularly in those who are premenopausal.

Proviral load, the number of integrated copies of HTLV-1 expressed as a proportion of peripheral blood mononuclear cells, has also been identified as a marker of disease progression. Whereas the viral load in an untreated patient with HIV infection increases as the disease progresses, the HTLV-1 proviral loads remains relatively stable. Symptomatic individuals have proviral loads at least 10 times greater than asymptomatic individuals and progress more rapidly, possibly due to increased activity of infected lymphocytes in the CNS. Unlike HIV infection, the proviral load is maintained through cell division rather than viral replication, resulting in a slower evolution.

Diagnostic Studies

The diagnosis of HAM/TSP requires the exclusion of other disorders that can cause a chronic, progressive spastic paraparesis including mass lesions within the spinal cord, extrinsic cord compression, multiple sclerosis, amyotrophic lateral sclerosis, vitamin deficiencies (e.g., vitamin B_{12}), syphilis, and HIV vacuolar myelopathy.

In addition to serologic testing for the presence of the virus and determination of the proviral load, the peripheral blood smear in HAM/TSP reveals atypical lymphocytes with convoluted nuclei, known as “flower cells.” Further serologic testing may show hypergammaglobulinemia, increased β_2-microglobulin, and an elevated $CD4^+$ T-cell count.

The CSF in patients with HAM/TSP demonstrates a lymphocyte-predominant pleocytosis and elevated CSF protein concentration in the setting of normal glucose levels. The magnitude of these abnormalities declines over the disease course. Oligoclonal bands, inflammatory markers, and HTLV-1-specific antibodies may also be present. A CSF proviral load greater than 10 percent and a ratio with the plasma proviral load of greater than 1:1 may distinguish HAM/TSP from asymptomatic disease.

MRI does not distinguish HAM/TSP from other demyelinating processes; spine MRI is normal most commonly. Brain MRI findings may include T2-weighted hyperintensities in the subcortical, deep, and periventricular white matter. These multifocal white matter lesions are associated with longer duration of disease and increased disability.

Treatment

Treatment options for HAM/TSP are limited due to a combination of factors including a disease burden that is highest in countries where access to care is limited and surveillance data are poor; little financial incentive for drug development for a relatively rare disorder; and difficulty in developing trials due to a limited understanding of disease pathogenesis.[15]

A wide array of interventions that lack efficacy have been tried in HAM/TSP. Corticosteroids are the most commonly prescribed drugs, and there is some evidence for efficacy in the short term.

Although associations between inflammatory cytokines and proviral load have been identified, there are few randomized, controlled trials of immunomodulatory drugs. Interferon-alpha has been tested in small series but the drug also is limited by a severe side-effect profile. The efficacy of other agents such as cyclosporine, azathioprine, and sulfasalazine remains unclear. The utility of treatment with monoclonal antibodies is uncertain. An investigational agent used for adult T-cell leukemia, mogamulizumab, may improve spasticity and CNS inflammation in some individuals with HAM/TSP. Although antiretroviral agents against HTLV-1 are effective in the laboratory, studies have failed to demonstrate a decrease in the proviral load, perhaps due to the lack of continuous replication cycles requiring reverse transcriptase in chronic HTLV-1 carriers.

Due to the lack of effective disease-modifying therapies, symptomatic management is the mainstay of treatment. Spasticity and muscle spasms can be relieved with a combination of physical therapy and muscle relaxants. Neuropathic pain is managed with gabapentin or tricyclic agents. The threshold for testing for and treating urinary tract infections should be low; urine acidification can decrease this risk. Oxybutynin can be used to relieve urinary urgency and frequency arising from bladder spasticity, and stool softeners help manage chronic constipation.

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CHAPTER

44

Neurologic Complications of Transplantation and Immunosuppressive Agents

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NEUROLOGIC COMPLICATIONS COMMON TO ALL TRANSPLANTATION TYPES
- Encephalopathy
- Seizures
- Cerebrovascular Complications
- Infections
  - *Bacterial*
  - *Viral*
  - *Fungal*
  - *Parasitic*
- Immune Reconstitution Inflammatory Syndrome
- Lymphoproliferative Disorders
- Autoimmune Disorders

HEMATOPOIETIC CELL TRANSPLANTATION
- Early Complications (<1 Month)
- Intermediate Complications (From Engraftment to 6 Months)
- Late Complications (Occurring Beyond 6 Months)

SOLID ORGAN TRANSPLANTATION
- Hepatic Transplantation
- Renal Transplantation
- Cardiac Transplantation
- Pulmonary Transplantation
- Pancreatic Transplantation
- Small Bowel and Multivisceral Transplantation

COMPLICATIONS OF IMMUNOMODULATORY THERAPIES
- Calcineurin Inhibitors
- Mammalian Target of Rapamycin Inhibitors
- Corticosteroids
- OKT3 Monoclonal Antibody
- Azathioprine
- Mycophenolate Mofetil
- Disease-Modifying Therapies for Multiple Sclerosis
- Immune Checkpoint Inhibitors
- Chimeric Antigen Receptor T-cell Therapy

Advances in solid organ and hematopoietic cell transplantation (HCT) have revolutionized the treatment of many previously fatal diseases. Immunologic and procedural innovations in tandem with the development of new immunosuppressive agents have increased the number, type, and durability of these transplantations. Post-transplant complications affecting the nervous system are particularly devastating in some cases. Neurology consultants are often asked to evaluate transplant recipients who have a wide array of neurologic signs and symptoms. An organized approach and astute clinical judgment are required to ensure proper management of these patients.

NEUROLOGIC COMPLICATIONS COMMON TO ALL TRANSPLANTATION TYPES

Encephalopathy

Altered mental status is one of the most common reasons for neurologic consultation in the post-transplantation period. The degree of encephalopathy can range from mild confusion to coma. A wide array of etiologies may be responsible including infection, metabolic disturbances, seizures, cerebrovascular disorders, and medication toxicity (discussed separately below). Postoperative hepatic or renal dysfunction may contribute to prolonged metabolism of sedative-hypnotic agents. Electrolyte abnormalities should be recognized as a potential etiology; in the case of hyponatremia, clinicians should be careful to ensure slow correction (<8 mmol/L in 24-hour period) in order to avoid osmotic demyelination syndromes.

Due to their prolonged illness course, decreased oral nutrition, and occasional caloric supplementation with total parenteral nutrition, transplant recipients are susceptible to the development of Wernicke's encephalopathy from thiamine deficiency. In addition to encephalopathy, patients may also exhibit other features of the classic triad including eye movement abnormalities and ataxia. Magnetic resonance imaging (MRI) may demonstrate symmetric increased

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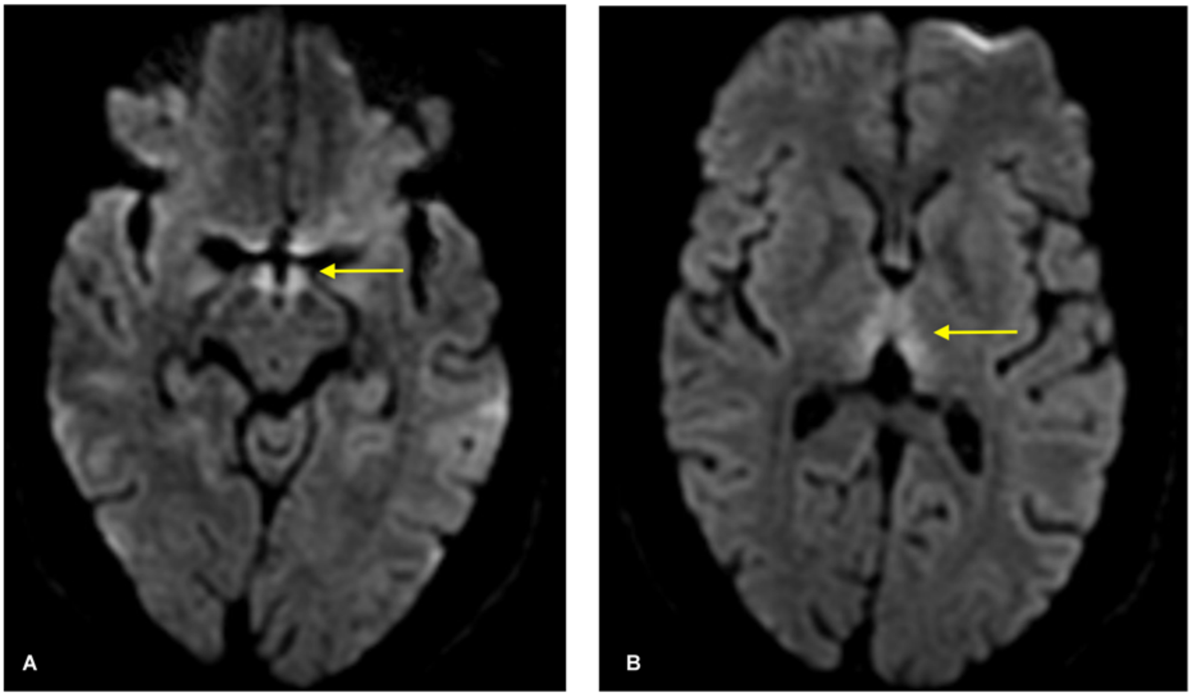

FIGURE 44-1 ■ Brain MRI findings in a patient with Wernicke encephalopathy. *A*, Axial diffusion-weighted image (DWI) demonstrating restricted diffusion in the mammillary bodies (*arrow*). *B*, Axial DWI through the thalami showing restricted diffusion of the dorsomedial thalamic nuclei bilaterally (*arrow*). Concordant T2 hyperintensities as well as gadolinium enhancement can be found in the same locations.

T2 signal intensity as well as contrast enhancement or restricted diffusion in the mammillary bodies, dorsomedial thalami, or periaqueductal area (Fig. 44-1), but cerebrospinal fluid (CSF) analysis is normal and EEG often demonstrates nonspecific diffuse slowing. Prompt supplementation with intravenous thiamine is imperative to reduce neurologic morbidity and prevent progression to Korsakoff syndrome.

Post-transplantation encephalopathy may also be caused by posterior reversible encephalopathy syndrome (PRES). While the syndrome preferentially affects the posterior cerebral regions (Fig. 44-2), variations do occur, most frequently involving the frontotemporal lobes and rarely the basal ganglia, brainstem, or thalami. Patients often present with headache, encephalopathy ranging from mild inattention to akinetic mutism or coma, seizures, or various visual syndromes. Transplant recipients are particularly vulnerable to developing PRES as they experience significant fluctuations in blood pressure, renal failure, and sepsis, all known risk factors for the development of the disorder.[1] Medications that commonly trigger PRES include the calcineurin inhibitors tacrolimus and cyclosporine, but the condition has also been described with other immunomodulatory therapies used in this population.[1] The patient's blood pressure need not be very high for occurrence of this syndrome, which appears to be related to the rate of change of blood pressure from baseline combined with a loss of cerebral autoregulation and endothelial dysfunction. Lowering of the blood pressure by any means will usually result in resolution of both the clinical syndrome and imaging abnormalities, although in some cases permanent neurologic sequelae can occur.

Seizures

Seizures are particularly common in the post-transplantation period. The most common causes of seizures are immunosuppressive agents (especially cyclosporine, tacrolimus, and OKT3), metabolic derangements, and hypoxic-ischemic injury. Infection, stroke, and tumor are less frequent causes of seizures in this population. Often, the seizure disorder is transient and requires no treatment other than reduction in the dose of offending medications, correction

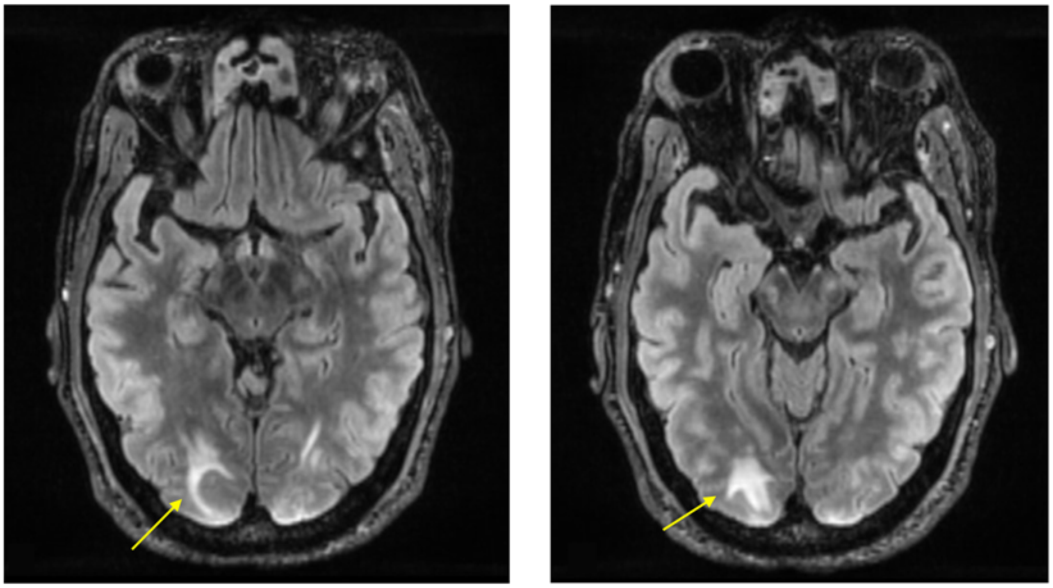

FIGURE 44-2 ■ Brain MRI of a hepatic transplant recipient with posterior reversible encephalopathy syndrome. Axial T2-weighted fluid-attenuated inversion recovery MRI demonstrating bilateral subcortical hyperintensities within the right greater than left occipital lobes (*arrows*).

of metabolic derangements, or treatment of underlying infection. Long-term therapy with antiepileptic drugs is undesirable in transplant recipients as interactions can occur with their immunosuppressive regimen; inducers of the hepatic cytochrome oxygenase P-450 system (e.g., carbamazepine, phenytoin) result in a decrease in the levels of many calcineurin inhibitors, necessitating dose adjustments. As such, if antiseizure medication is required, selection of a nonenzyme-inducing agent such as levetiracetam, lacosamide, or valproic acid is often preferable, although in liver transplantation, valproic acid should be avoided given potential hepatotoxicity.

Cerebrovascular Complications

Patients undergoing both hematopoietic cell and solid organ transplantation (SOT) are at risk of cerebrovascular events especially during the surgical and postoperative periods. Cerebral ischemia occurs as a result of arrhythmias, hypercoagulable states, underlying atherosclerosis, cardiac emboli, or prolonged hypoxic injury. Both ischemic and hemorrhagic stroke may occur in the setting of PRES and thus perioperative blood pressure management in this population is critical. Transplanted organ-specific cerebrovascular complications will be highlighted below.

Infections

Patients receiving long-term immunosuppression are at an increased risk of developing infections. Neurologic infections are particularly clinically relevant as they have the potential to cause significant morbidity and mortality in an immunocompromised host. Nearly every conceivable type of infection—bacterial, viral, fungal, and parasitic—has been reported to infect transplant recipients, but about 75 percent of cases are due to *Listeria monocytogenes*, *Cryptococcus neoformans*, or *Aspergillus fumigatus*.[2,3]

One important risk factor for infection is the immunosuppression necessary to prevent rejection of the allograft. The single most important risk factor for developing post-transplantation central nervous system (CNS) infection is the magnitude and length of immunosuppression. In addition, after transplantation, patients often have indwelling catheters, endotracheal tubes, and other portals of entry for infection. Patients' underlying diseases and their complications also contribute to the net state of immunosuppression. Certain infections themselves, especially viruses, also cause suppression of the immune system, in turn leading to increased susceptibility to additional infections.[2]

CNS infections in immunocompromised hosts may be difficult to recognize. The usual signs of infection, such as fever and meningismus, may be subtle or

TABLE 44-1 ■ Notable Infectious Pathogens Affecting the Nervous System in Recipients of Hematopoietic Cell and Solid Organ Transplantation

Bacteria	Viruses	Fungi	Parasites
Listeria monocytogenes	Varicella-zoster virus	*Aspergillus* species	*Toxoplasma gondii*
Mycobacterium tuberculosis	Epstein–Barr virus	Mucorales	
Nocardia species	Cytomegalovirus	*Cryptococcus* species	
	Human herpesvirus 6		
	Herpes simplex virus type 1		
	John Cunningham (JC) virus		
	West Nile virus		

absent, as they depend on a vigorous immune response.[2] As a result, clinicians should have a high index of suspicion for infectious causes of neurologic symptoms in transplant recipients. Evidence of infection outside the nervous system may provide clues to a possible etiology. For example, skin lesions may be found to harbor *Cryptococcus* and co-existent lung infection suggests *Aspergillus*, *Nocardia*, or *Cryptococcus*.

Specific infectious pathogens complicating the post-transplantation period depend on a number of factors including the time from receipt of the graft, the specific immunosuppressive regimen, exposure and travel history, and the type of transplantation itself. Common culprit infectious organisms particular to each type of transplanted graft are discussed below. Table 44-1 lists important pathogens affecting the nervous system in recipients of both hematopoietic cell and SOT.

BACTERIAL

Although transplant recipients are at risk of the typical causes of bacterial meningitis including *Streptococcus pneumonia* and *Neisseria meningitidis*, they are particularly susceptible to less common organisms including *L. monocytogenes*.[3,4] The most common neurologic manifestation of *L. monocytogenes* is acute meningoencephalitis with a predilection for the brainstem and cerebellum. Unfortunately, the organism is often difficult to isolate and may present with a lymphocytic pleocytosis, unlike most bacterial meningitides that feature a neutrophilic predominance. Clinicians should maintain a high index of suspicion for *Listeria* infections and consider empiric treatment with ampicillin. Immunosuppressed patients are also at risk of infection with *Nocardia* spp., particularly in the first year after transplantation when immunosuppression is highest in order to prevent graft rejection. This gram-positive bacteria most commonly results in pulmonary infection but dissemination to the brain in the form of single or multiple cerebral abscesses may occur.[3] Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) reduces the risk of nocardiosis but is not commonly employed for this purpose. With CNS involvement, treatment with prolonged IV TMP-SMX and imipenem is recommended with clinical and radiologic monitoring for treatment response.

VIRAL

Several different viral infections may occur in recipients of transplants. In cases of cytomegalovirus (CMV) and Epstein–Barr virus (EBV), these infections themselves may predispose patients to infections with additional opportunistic organisms including *Listeria*, *Aspergillus*, and *Nocardia*.[2,3] CMV results in a spectrum of neurologic complications including retinitis, ventriculoencephalitis, and polyradiculitis with a predilection for the caudal spine. Diagnosis is made with CSF PCR and treatment typically includes a combination of ganciclovir and foscarnet. Infection with EBV may similarly result in an encephalitic or myeltic picture, but also predisposes this patient population to post-transplant lymphoproliferative disorder (PTLD). Treatment of EBV involves ganciclovir for infectious presentations and immunosuppression with B-cell depleting therapies for EBV-associated lymphoproliferative disorders.

Varicella-zoster virus can involve both the central and peripheral nervous systems. Due to widespread use of antiviral prophylaxis in the pretransplantation period, complications related to reactivation of varicella-zoster virus now emerge later than in the past. The most common complication is cutaneous zoster, but transverse myelitis, vasculitis, and polyneuritis also occur.[3] Often when a dermatomal rash is absent, the etiology of the neurologic syndrome is uncertain and confirmation of VZV is necessary using CSF VZV IgM and IgG along with PCR testing. Treatment with IV acyclovir is recommended in this immunocompromised population.

Progressive multifocal leukoencephalopathy (PML), a severe demyelinating disorder of the CNS resulting from reactivation of polyomavirus JC virus (JCV), may develop in recipients of both hematopoietic cell and SOT. Patients present with subacute neurologic deficits that reflect the area of white matter injury, typically sparing the optic nerves and spinal cord. MRI demonstrates multifocal, often asymmetric, white matter lesions involving the subcortical U fibers but without mass effect or evidence of enhancement (Fig. 44-3). Diagnosis is confirmed by positive JCV in the CSF but, given its poor sensitivity, brain biopsy is sometimes necessary and remains the gold standard. Unfortunately, there is no proven effective treatment for PML, though reducing immunosuppression is recommended and emerging therapies including checkpoint inhibitors are being explored.[3] A reduction in immunosuppression may occasionally lead to the development of immune reconstitution inflammatory syndrome (IRIS) with clinical worsening of PML as well as new enhancement on MRI, often necessitating steroids.

FUNGAL

CNS cryptococcal disease often presents with headache, altered mental status, or cranial neuropathies, resulting from meningitis with obstructive or nonobstructive hydrocephalus. Involvement of the parenchyma in the form of cryptococcomas, often located in the basal ganglia or midbrain, is a more rare presentation. Clinicians should be careful to accurately measure opening pressure as patients will often have increased intracranial pressure necessitating serial lumbar punctures and occasionally more permanent CSF drainage in order to prevent optic nerve damage. CSF studies typically demonstrate a mononuclear

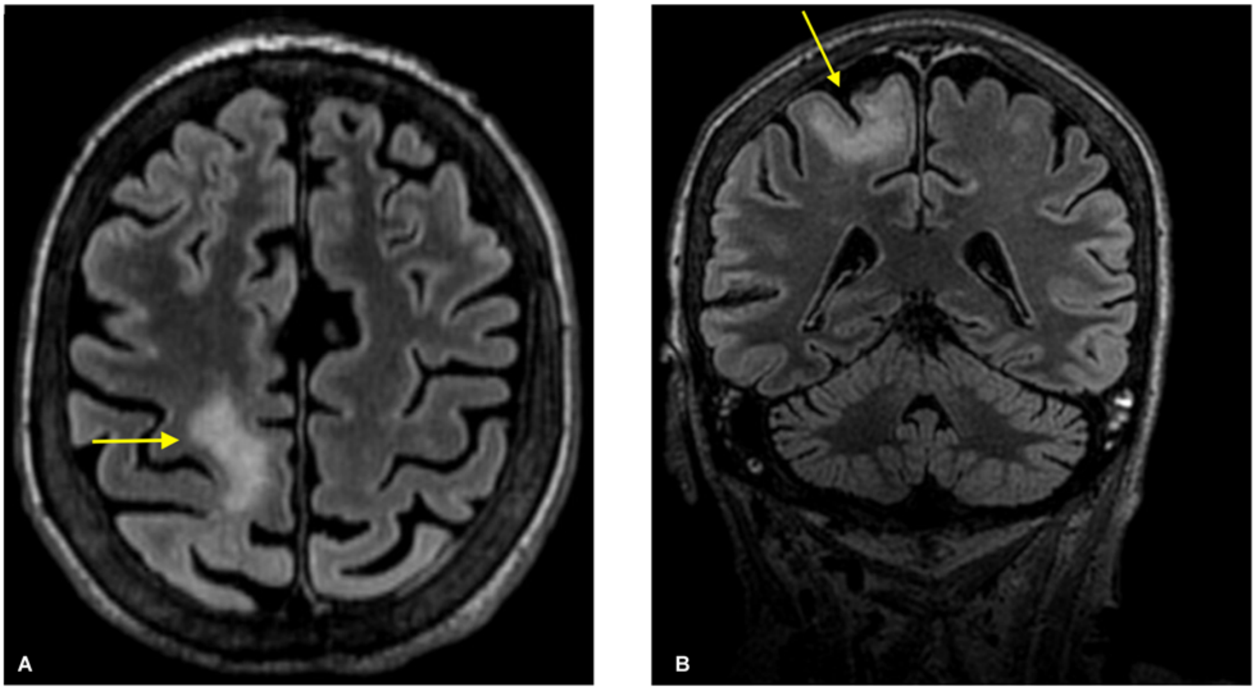

FIGURE 44-3 ■ Brain MRI in a patient with progressive multifocal leukoencephalopathy. *A*, Axial fluid-attenuated inversion recovery (FLAIR) and *B*, coronal FLAIR cuts demonstrating a T2 hyperintensity predominantly involving the right precentral gyrus and right superior frontal gyrus extending into the posterior frontal lobe white matter (*arrows*). There is no associated mass effect as is often the case in PML and there was no restricted diffusion or contrast enhancement on other sequences.

pleocytosis, elevated protein, and low glucose. Confirmation of the diagnosis is made with detection of cryptococcal antigen using latex agglutination or ELISA or India ink staining for detection of encapsulated yeast organisms.[2,5] In addition to *Cryptococcus*, clinicians should consider endemic fungi when individuals present with chronic meningitis and a history of travel to certain geographic areas—*Blastomyces dermatitis* (midwestern United States and Canadian provinces bordering the Great Lakes), *Histoplasma capsulatum* (Ohio River valley and the lower Mississippi River region), and *Coccidioides* spp. (California and southwestern United States).[5]

Infection with *Aspergillus* spp. may result in CNS manifestations and occurs in the setting of disseminated infection or from local extension from the paranasal sinuses. Patients typically present with progressive focal neurologic symptoms or seizures secondary to underlying abscess formation but may also develop acute deficits from cerebral ischemia or hemorrhage related to mycotic aneurysm development. Although candidemia is not uncommon in immunosuppressed patients, involvement of the nervous system is rare.[5]

PARASITIC

Although often overlooked, parasitic infection can also lead to significant neurologic morbidity and mortality in transplant recipients. Infection may occur via transmission from an infected graft, be acquired de novo by the immunosuppressed host, or occur due to reactivation in the setting of impaired cellular immunity.[3,6] *Toxoplasma gondii* reactivation represents the most common parasite with neurologic complications in this population. The incidence of neurologic complications of *T. gondii* is offset by the use of TMP-SMX prophylaxis in the post-transplantation period. Patients typically present with headache with or without focal neurologic symptoms but *T. gondi* reactivation can also cause extra-CNS complications, most commonly chorioretinitis and pneumonitis. Imaging demonstrates tropism for the basal ganglia and thalamus, revealing multiple ring-enhancing lesions with perilesional edema in the deep gray matter. A presumptive diagnosis is often made in patients seropositive for anti-*Toxoplasma* IgG antibodies in the presence of a typical clinical syndrome and imaging. Empiric therapy with sulfadiazine and pyrimethamine is preferred, though various alternative regimens exist.[3]

Immune Reconstitution Inflammatory Syndrome

Although well-recognized in HIV patients receiving highly active antiretroviral therapy, IRIS may also occur in recipients of hematopoietic cell and SOTs in the context of immunosuppression withdrawal. The condition features an intense inflammatory response that occurs as immune function is restored in the presence of an underlying opportunistic infection (typically *Cryptococcus*, tuberculosis, or PML).[7] When transplanted patients develop symptoms of CNS infection, immunosuppressive medications are often decreased to allow for a more robust immune response, leading to an increased risk of IRIS. Clinical presentation typically consists of paradoxical worsening of symptoms of a known infection or unmasking of a previously unrecognized infection in this clinical setting. As symptoms may mimic those of the original infection, the diagnosis of CNS IRIS is often difficult to make, especially since treatment failure, antimicrobial resistance, and additional neurologic infections are other important diagnostic considerations.[7] Management of IRIS involves prompt treatment of underlying infection and consideration of adjunctive corticosteroids to reduce the severe inflammatory response, although no related randomized controlled studies exist.

Lymphoproliferative Disorders

The chronic use of immunosuppressive agents to prevent allograft rejection increases the long-term risk of malignancy. Lymphoproliferative syndromes may occur in recipients of both hematopoietic cell and SOTs, often in the first year. The term PTLD is used to describe a wide spectrum of disorders characterized by abnormal proliferation of B cells (less commonly T cells) ranging from "benign" diffuse polyclonal lymphoid hyperplasia to malignant monoclonal lymphoma. CNS involvement occurs in up to 15 percent with PTLD and is the most common type of malignancy involving the brain in transplant recipients.[6,8] B-cell malignancies in transplanted patients are strongly associated with EBV infection unlike primary CNS lymphoma in immunocompetent patients. These B-cell lymphomas arise in deep areas of the brain with a propensity for the perivascular spaces. CNS lymphoma is distinguished radiographically from PML on brain MRI by its significant mass effect, restricted diffusion secondary to hypercellularity, and enhancement. Therapy for PTLD consists primarily of reduction of immunosuppression and a combination of conventional cytotoxic chemotherapy, radiotherapy, and often B-cell depleting agents. Unfortunately, the mortality rate remains high with CNS involvement leading to a poorer prognosis.[6,8]

Autoimmune Disorders

Several autoimmune disorders have been described in the late post-transplantation period, most of which are antibody-associated organ-specific conditions such as autoimmune thyroiditis or myasthenia gravis. These secondary autoimmune disorders may occur as a result of an underlying propensity for autoimmunity but also due to immune dysregulation in the setting of immunosuppression.

HEMATOPOIETIC CELL TRANSPLANTATION

The indications for HCT currently involve a broad range of pathologies including various hematologic malignancies, autoimmune diseases, inborn errors of metabolism, and congenital immune deficiencies. In an effort to restore bone marrow function, HCT involves the infusion of multipotent hematopoietic stem cells after a host is treated with chemotherapy with or without irradiation.

Three principal factors underlie a given patient's risk of post-HCT complications: conditioning regimen, graft type, and source of stem cells. The conditioning regimen describes the chemotherapeutic and radiation treatments delivered immediately prior to transplant. These conditioning regiments are classified as either full-intensity myeloablative or nonmyeloablative. Nonmyeloablative reduced intensity conditioning is associated with a lower risk of infection and relies on a graft-versus-tumor effect to compensate for the inherent increased risk of malignancy relapse. Graft types include autologous HCT, which requires the extraction of stem cells from the host and their reinfusion after myeloablative therapy, and allogeneic transplants that involve the infusion of cells from an HLA-compatible donor who can be syngeneic (monozygotic twins), related, or unrelated with a close degree of HLA matching. In the current therapeutic era, stem cells are most commonly harvested from peripheral blood and bone marrow, though umbilical cord blood-derived cells are also sometimes used.

Despite advances in technique, HCT continues to result in a number of neurologic complications, significantly contributing to morbidity and mortality. Recipients of an allogenic graft, notably one with marked HLA disparity, have higher rates of these side effects.[9] Neurologic complications common to transplant recipients are relevant in this population, but HCT carries its own unique risk profile. Specific issues emerge at different time-points from transplantation and can be organized accordingly: early (i.e., within the first month), intermediate (i.e., 1 to 6 months), and late (i.e., occurring beyond 6 months).[9]

Early Complications (<1 Month)

Neurologic complications during the stem cell harvesting period are infrequent, although some patients undergoing autologous HCT may experience exacerbation of underlying autoimmune diseases. During the conditioning phase, patients receive various alkylating agents with or without small doses of total-body irradiation and are prone to neurologic complications including encephalopathy, seizures, opportunistic infections, and stroke. They may also experience side effects from prophylactic antibiotic regimens as well as the medications used to prevent graft-versus-host disease (GVHD).

Patients undergoing HCT are usually more severely immunosuppressed at the time of transplant than those undergoing SOT due to both the underlying hematologic malignancy and the specific myeloablative conditioning regimen used. The granulocytopenic state continues for approximately 1 month until the new marrow begins to function. Typical clinical indicators of a neurologic infection may be absent during this period due to the host's impaired immune response, and as such physicians should be vigilant for any neurologic symptoms.

In the pre-engraftment period, patients are particularly vulnerable to bacterial infections, notably enteric gram-negative organisms including *Klebsiella* spp. and *Escherichia coli* as well as gram-positive cocci introduced via indwelling vascular catheters. More rare causes of atypical bacterial infections such as *Listeria* and *Nocardia* may also occur, although infrequently due to antibiotic prophylaxis. Neutropenic patients are also at risk for various viral infections including herpesviridae and polyomaviridae. Clinicians must recognize symptoms of post-transplant acute limbic encephalitis, a syndrome of anterograde amnesia, syndrome of inappropriate antidiuretic hormone secretion, mild CSF pleocytosis, hippocampal MRI hyperintensities, and EEG abnormalities with or without clinical seizures. While various infectious and autoimmune etiologies exist for this constellation of features, HHV-6 is the most well-recognized culprit in the acute post-transplant period and results from reactivation of previous host infection. Treatment relies on appropriate antiepileptic drug therapy as well as antiviral medications such as ganciclovir and foscarnet.

During the pre-engraftment period, patients are also at risk of invasive fungal infections. *Aspergillus* spp. are the most common, and the clinical presentation may be quite variable including headaches, seizures, focal neurologic symptoms, and altered mental status. Typical neuroimaging features include multiple ring-enhancing lesions associated with restricted diffusion on MRI, often with surrounding hemorrhage.[5] Abscesses involving the corpus callosum and brainstem are particularly suggestive of aspergillosis. Due to its angioinvasive nature, ischemic infarcts, mycotic aneurysms, and vasculitis may also be present. Since infection of the CNS often results from invasive rhinosinusitis, imaging commonly demonstrates intracerebral extension from the paranasal sinuses with dural enhancement.

Since the diagnostic yield of blood cultures is low and brain biopsy of deep or eloquent regions remains difficult, clinicians should consider serum and CSF markers of fungal infection (e.g., galactomannan antigen and β-D-glucan) in support of a suspected diagnosis of CNS aspergillosis. Voriconazole is the current first-line treatment for invasive aspergillosis, although for patients with severe disease, combination therapy with echinocandin for the first 2 weeks may be recommended.

Fluconazole prophylaxis has no activity against *Aspergillus* spp. and only reduces the risk of invasive candidiasis, which is the most common systemic fungal infection in HCT recipients. CNS involvement with disseminated candidemia, remains rare.[5] When it does occur, *Candida* spp. typically result in a meningitic picture. Multiple cerebral abscesses may occur in immunocompromised hosts. The treatment of choice for this organism is liposomal amphotericin B, with or without flucytosine, followed by step-down therapy with oral fluconazole.

Patients in the pre-engraftment period are often thrombocytopenic, and hemorrhagic complications may therefore occur. Subdural hematoma is the most frequent CNS hemorrhagic disorder in this setting, although intraparenchymal and subarachnoid hemorrhage have also been described.[9] Ischemic stroke may also complicate the early HCT period and has been linked to infusion of stem cells with dimethyl sulfoxide cryopreservative. Stroke can also occur in the setting of various CNS infections, notably with bacterial basilar meningitis, VZV-vasculopathy or the angioinvasive fungal organisms such as *Aspergillus* spp. and *Mucormycosis*.

Intermediate Complications (From Engraftment to 6 Months)

As patients enter the second month post-HCT, there is progressive recovery of cell-mediated immunity, and therefore the risk of bacterial infection decreases dramatically. Viruses and infections with opportunistic organisms predominate during this period. The most common viral infections and their typical neurologic presentations are detailed in Table 44-1. In this intermediate phase, consultants will frequently encounter transplant recipients with neurologic manifestations of herpesviruses including EBV, CMV, and VZV. Patients are at risk of CNS infection with *T. gondii*, particularly 2 to 4 months post-transplantation, with reactivation of latent parasitic infection being the most common mechanism.

Apart from increased susceptibility to infection in the first 100 days post-transplantation, recipients of an allogenic graft may also develop symptoms of acute GVHD. This complication results from an attack on host tissue by immunologically competent lymphocytes. Although most frequently associated with bone marrow transplantation, the condition can occur occasionally after liver transplantation and, in severely immunosuppressed patients, following lymphocyte-containing blood transfusions.[6] Patients receive a cocktail of immunosuppressive agents to mitigate this risk of post-transplantation immunologic reconstitution. Acute GVHD is characterized by rash, diarrhea, and liver dysfunction, typically with no associated neurologic complications. Symptoms of chronic GVHD may develop in the intermediate period and neurologic complications are often a late finding as discussed below.[9,10]

Late Complications (Occurring Beyond 6 Months)

Features of chronic GVHD occur after the 100-day mark, although this time designation is arbitrary and symptoms may occur before this period. In comparison to acute GVHD, several neuromuscular and CNS complications occur in chronic GVHD patients. Distinctive manifestations implicating the peripheral nervous system mainly involve myositis, whereas disorders of the peripheral nerve and neuromuscular junction occur less frequently and are usually accompanied by other organ involvement.[6,10] CNS manifestations are not typically associated with chronic GVHD and alternative diagnoses should always be considered.[10] The management of these neurologic complications involves treatment with immunosuppressive agents including corticosteroids with the long-term goal of a steroid-sparing regimen.

Recipients of a HCT usually require less long-term immunosuppressive therapy than those undergoing other types of transplantation, and sometimes immunosuppression may be discontinued after successful engraftment if no GVHD is present. Perhaps as a consequence, the prevalence of PTLD with CNS involvement is lower in this population.

Despite less intensive immunosuppression, HCT recipients remain at risk for infection. Most lingering infections are caused by viruses and include progressive chorioretinitis from CMV and EBV-related B-cell lymphoproliferative disease.[2,3] Opportunistic infections that develop more than 6 months after HCT tend to occur in patients with chronic allograft rejection. Such patients are maintained on higher than usual doses of long-term immunosuppressive agents such as corticosteroids and have received additional antirejection therapy, usually with OKT3, antithymocyte globulin, or antilymphoblast globulin. This cohort is at the greatest risk of developing opportunistic CNS infections, most commonly *Cryptococcus*, *Listeria*, and *Nocardia* spp.

Cerebrovascular complications are also a relatively frequent late problem after HCT with nonbacterial thrombotic endocarditis (NBTE) or infective endocarditis as common etiologies. The mechanism by which NBTE occurs in HCT recipients is unknown, although there is an association with disseminated intravascular coagulation and other acquired hypercoagulable states. Despite prolonged thrombocytopenia and abnormalities in coagulation, intracerebral hemorrhage is relatively rare in the late post-HCT period.

SOLID ORGAN TRANSPLANTATION

SOT involves the transfer of an entire organ from a tissue-matched deceased donor or a single kidney, partial liver, or intestinal tissue from a related or unrelated matched living donor. Neurologic complications are common in SOT recipients and most frequently consist of those described earlier including encephalopathy, seizure, infection, and cerebrovascular events.

Few neurologic complications occur exclusively in SOT recipients. Infectious complications related to donor organ-associated infections, however, are noteworthy. Donors undergo an extensive infectious work-up prior to SOT and consequently most donor-derived infectious disease transmission events are not unexpected. Unfortunately, despite donor screening, unforeseen transmission events occasionally occur either due to insensitivity of diagnostic testing or as a result of rare or emerging pathogens for which screening does not routinely occur. Some of the more notable cases of donor-associated infections transmitted include West Nile virus, rabies, lymphocytic choriomeningitis virus, and *Balamuthia mandrillaris*.

Hepatic Transplantation

Hepatic transplantation is used to treat acute liver failure (e.g., due to viral or drug-induced hepatitis), advanced cirrhosis due to cholestatic diseases (e.g., primary biliary cirrhosis and sclerosing cholangitis), hepatocellular disorders (e.g., alcoholic or viral hepatitis), hepatic malignancies (both primary and metastatic disease), and metabolic disorders (e.g., α_1-antitrypsin deficiency, Wilson disease, familial amyloid polyneuropathy, or acute intermittent porphyria). Although liver transplantation can improve and sometimes cure patients with end-stage hepatic disease, neurologic complications are more common than in any other type of SOT.

Due to organ shortages, patients frequently wait a considerable time for liver transplantation. As a result, by the time of transplantation they are often critically ill, with many having some degree of preoperative metabolic encephalopathy due to chronic liver failure. Patients with acute liver failure also frequently present with altered mental status in the setting of hyperammonemia, with MRI demonstrating symmetric T2-hyperintensities and restricted diffusion most commonly within the insular and cingulate cortex but

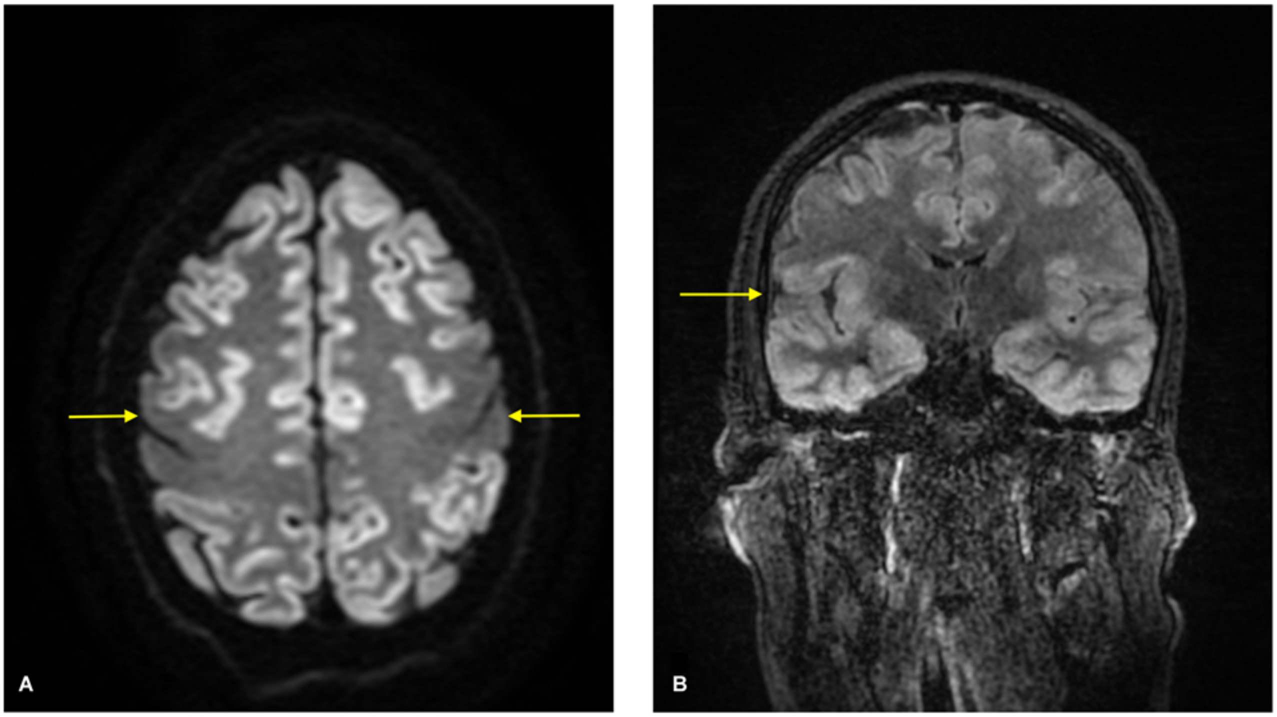

FIGURE 44-4 ■ Brain MRI in a patient with a hyperammonemic encephalopathy. *A*, Axial diffusion-weighted image demonstrating prominent cortical restricted diffusion with relative sparing of the perirolandic cortex (*arrows*). *B*, Coronal T2 fluid-attenuated inversion recovery concordant hyperintensities with prominent involvement of the insula (*arrow*).

with more diffuse cortical involvement in severe cases, typically with relative sparing of the perirolandic and occipital regions (Fig. 44-4).

Encephalopathy following hepatic transplantation is frequently multifactorial and clinicians should be mindful that seizures may occur in the perioperative period and be contributory. Seizures may be related to immunosuppressive medications, hypoglycemia, electrolyte abnormalities, or PRES.

Altered mental status may also arise secondary to cerebral edema and intracranial hypertension, which occur to some degree in almost all patients with severe hepatic encephalopathy. Medical management of increased intracranial pressure commonly necessitates hyperosmolar therapy, sedation, neuromuscular blockade, and sometimes hypothermia, though the evidence for the latter is less robust. Transplantation and restoration of normal liver function is the key to reducing intracranial pressure definitively.

Patients with chronic liver disease are at particularly high risk of osmotic demyelination resulting in a clinical syndrome classically referable to the pons (central pontine myelinolysis) but which can involve other structures including the basal ganglia, white matter, or thalamus. The clinical manifestations of these two entities are further discussed in Chapter 17. During the perioperative liver transplantation period, patients often experience large fluid shifts and resultant abrupt changes in serum sodium concentrations that may lead to this disorder. In the cirrhotic population, osmotic demyelination may occur in the absence of the marked sodium fluctuations and physicians should therefore be meticulous in their management of electrolytes and volume status. No specific treatment exists for this disorder and supportive care is the current standard.

Because of substantial blood loss intraoperatively during the transplantation procedure, patients often require significant replacements of packed red blood cells and electrolytes. Due to prolonged periods of hypotension, patients may rarely experience hypoxic-ischemic damage to the brain or watershed infarctions. Intraoperative cerebral infarctions may also be caused by air embolism or artery-to-artery embolism.

Peripheral nerve injuries may also occur during the transplantation procedure. Damage to the brachial plexus may be caused by axillary dissection performed for the placement of femoral–axillary venous bypasses. Likewise, lymphatic vessels can be damaged during the venous–venous bypass procedure resulting in a lymphocele that leads to secondary injury to the femoral nerve. Right phrenic nerve injury can occur during the transplant and results in hemidiaphragmatic weakness. Other neuropathies may occur from catheterization injuries, nerve compression, and surgical retraction.

The side effects of immunosuppression after liver transplantation are similar to those occurring in other types of transplantations. Calcineurin inhibitors are most commonly used and neurologic complications are more common and severe in this population. Additionally, the frequency of PTLD with CNS involvement in recipients of a hepatic graft is second only to cardiac and combined heart–lung transplantations.

Renal Transplantation

Since the first successful human kidney transplantation in 1954, the procedure has developed into the treatment of choice for patients with end-stage renal disease. The kidney is the most frequently transplanted solid organ worldwide, and there is now nearly a 100 percent 1-year survival rate. The indications for renal transplantation are numerous and include glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, amyloidosis, and diabetic and hypertension-related renal disease. Neurologic complications are associated with increased morbidity and mortality.

The toxic effects of pretransplantation uremia may cause subclinical neurologic impairment and leave the nervous system vulnerable to subsequent injury following transplantation. In addition, renal transplant candidates often suffer from many underlying vascular diseases, notably diabetes and hypertension, which themselves are associated with accelerated atherosclerosis and an elevated risk of cerebrovascular complications. The most common neurologic complications post-transplantation in this patient population are cerebrovascular, occurring in approximately 10 percent of all recipients of renal grafts.[11] Similar to cirrhotic patients, those with chronic kidney disease are susceptible to osmotic demyelination, and careful attention to and correction of hyponatremia is crucial.

The renal transplantation procedure itself is relatively benign. Neurologic complications, other than those caused by anesthesia or intraoperative hypotension, consist mainly of peripheral nerve injuries. Acute femoral neuropathy complicates a minority of kidney transplantations, with most patients presenting with hip flexion and knee extension weakness along with paresthesias over the anteromedial thigh and medial calf immediately following surgery, or in the early postoperative period. This acute femoral neuropathy likely results from a “steal” phenomenon with secondary nerve ischemia during anastomosis of the iliac artery and the graft renal artery, and prolonged anastomosis increases its risk. Injury to the lateral femoral cutaneous nerve due to compression caused by retractors may also complicate the transplant. The clinical outcomes for both of these mononeuropathies remain favorable, with symptoms often resolving in weeks to months. In a few patients, the caudal spinal cord is supplied by branches of the internal iliac arteries rather than by intercostal arteries; in these patients, spinal cord ischemia may result when the iliac artery is used to supply blood to the allograft.

Acute rejection of the renal allograft can produce an encephalopathy presenting as a nonfocal exam with headache, altered mental state, and seizures. Systemic manifestations may include fever, weight gain, renal failure, and swelling and tenderness of the graft. This syndrome has been described only in renal transplantation, and the mechanism is unclear; soluble neuroactive immune factors such as cytokines released during the rejection process may play a role. Of note, a similar syndrome occurs as a side effect of OKT3.

Cardiac Transplantation

Cardiac transplantation is used to treat medically intractable dilated, hypertrophic, restrictive, and ischemic cardiomyopathies, as well as some cases of rheumatic heart disease. These conditions predispose patients to embolic ischemic events, brain hypoperfusion, and hypoxia. During surgery, patients are often placed on cardiopulmonary bypass for several hours and may be subjected to long periods of hypotension and hypoxia, resulting in watershed-distribution infarcts. Additionally, cardiac transplant recipients often have a number of vascular risk factors, making them susceptible to ischemic stroke in the perioperative period. These patients are also prone to paradoxical embolic disease and air emboli during the surgery itself. These ischemic insults may present with either focal neurologic deficits or as a nonfocal encephalopathy, the latter especially when an embolic shower is the underlying etiology. Seizures may complicate any of these cerebrovascular events and often contribute to altered mental status.

Peripheral nerve injuries are another relatively common complication of the transplantation procedure. The most frequently encountered lesions are brachial plexus injuries caused by retraction of the chest wall. The phrenic nerve also may be damaged by retraction, during the dissection of nearby structures, or from the practice of packing the heart in an ice-cold slush for myocardial protection during the transplantation.[6]

Although the pattern and timetable of CNS infections are similar to those in other types of transplantations, the side effects of immunosuppression are more common and severe in cardiac transplant recipients because higher doses of immunosuppressive agents are often involved. *Toxoplasma* infections account for a higher percentage of CNS infections than in other transplantations as the parasite may reside in the donor myocardium itself.[2,3,6] To reduce the risk of *T. gondii* infection, many cardiac transplant programs suggest lifelong prophylactic treatment with trimethoprim-sulfamethoxazole.

Pulmonary Transplantation

Lung transplantations are used to treat a variety of end-stage pulmonary diseases including emphysema, other severe chronic obstructive pulmonary diseases, cystic fibrosis, α_1-antitrypsin deficiency, and idiopathic pulmonary fibrosis. Although the first successful lung transplantation was performed over 30 years ago, recipients of pulmonary grafts continue to have the highest mortality rate among all SOTs and neurologic complications portend a poorer prognosis.[12] Lung and combined lung–heart transplants require the largest doses of short- and long-term immunosuppressive agents of any SOT, therefore putting this population at a higher risk for infectious and lymphoproliferative disorders involving the CNS. The most common neurologic complications in lung transplant recipients are perioperative stroke, seizures, and a multifactorial encephalopathy often related to chronic hypoxia.[12]

Peripheral nervous system involvement can also complicate lung transplantation. Of these, phrenic nerve injury during the transplantation surgery and critical illness neuropathy/myopathy are the most common. These complications frequently lead to prolonged hospitalizations.

Pancreatic Transplantation

Pancreatic transplantations are occasionally performed in patients with type 1 diabetes mellitus with extensive end-organ damage. Most pancreas transplantations are performed in conjunction with renal transplantations, either simultaneously or in patients who already have a functioning renal transplant. The principal objectives of this procedure are to render diabetic patients independent of insulin while reducing secondary complications and improving quality of life. Whole-pancreas transplants allow patients to become euglycemic within hours of surgery, and the procedure has a greater than 90 percent graft survival rate at 1 year.

Given the advanced nature of patients' diabetes, neurologic complications are common even prior to surgery and frequently include peripheral neuropathy, autonomic changes, and macrovascular complications such as cerebrovascular disease. Several studies have suggested that transplantation might not only halt progression of polyneuropathy but also lead to improvement of clinical symptoms and nerve conduction studies. Neurologic complications directly related to the transplantation procedure are generally rare. Global cerebral ischemia is the most frequently observed serious postoperative neurologic side effect which may be a consequence of the surgery itself combined with advanced atherosclerosis and autonomic neuropathy secondary to end-stage diabetes and renal dysfunction.

Small Bowel and Multivisceral Transplantation

The most common condition leading to small bowel transplantation is a short bowel syndrome following intestinal resection in the setting of Crohn disease, trauma, mesenteric thrombosis, or malignancy. This patient population may suffer from a number of baseline neurologic complications secondary to metabolic derangements including various water- and fat-soluble vitamin deficiencies as well as hypocalcemia and hypomagnesemia. Neurologic complications of small bowel transplantation are similar to other types of SOT. A more aggressive immunosuppression regimen is required in this cohort due to the underlying enhanced immunogenicity of the gut leading to increased risk of infections, typically fungal, in the early post-transplantation period.

COMPLICATIONS OF IMMUNOMODULATORY THERAPIES

A variety of immunosuppressive agents are used in the setting of HCT, SOT, and in the treatment of autoimmune neurologic disorders. The medications themselves as well as the resulting immunosuppressive effect may result in neurologic complications. The major neurologic complications of these therapies include direct neurotoxicity, infections, and the development of new malignancies (Table 44-2).[6,13]

Calcineurin Inhibitors

Cyclosporine and tacrolimus, both calcineurin inhibitors, are the most commonly used immunosuppressive agents in the setting of SOT, both for maintenance of immunosuppression and in the treatment of acute organ rejection.[6] These agents bind to calcineurin and selectively inhibit both helper and cytotoxic T cells by blocking antigen-induced T-cell activation.[13] Renal and hepatic toxicity along with hypertension are the most serious systemic complications of these medications, although neurologic side effects occur in up to half of patients. While neurologic complications are slightly more common with tacrolimus, both therapies result in almost identical side effect profiles.[6] Higher blood levels of calcineurin inhibitors are generally associated with side effects, but there is no simple correlation between serum levels and the development of any specific neurologic complication, and symptoms may occur even with normal levels. Enzyme-inducing anticonvulsants, such as phenytoin and carabamazepine, decrease blood levels of tacrolimus and cyclosporine by inducing hepatic metabolism and may increase the risk of graft rejection as a result. Several other medications interfere with the metabolism of these drugs and may lead to higher serum concentrations.

Tremor is the most common neurologic complication of calcineurin inhibitors. It is usually mild and develops within days of initiation in up to half of patients.[13] Headache represents another common neurologic side effect, occurring in approximately one-third of patients who receive parenteral tacrolimus; oral administration is less commonly associated with headaches.

Most of the serious neurologic toxicity of calcineurin inhibitors results from their tendency to produce hypertension. The hypertension that complicates these medications is due in part to renal toxicity and, to a larger extent, stimulation of the sympathetic nervous system. The encephalopathy that results is better correlated with the rate of change in blood pressure from the patient's baseline level than with an absolute value.[13] Calcineurin inhibitor-related neurotoxicity may be thought of as a forme fruste of hypertensive encephalopathy or PRES, the clinical spectrum and radiologic findings of which were described earlier.

In addition to their vascular effects, calcineurin inhibitors are also epileptogenic. Recipients may experience focal or generalized seizures, both of which are usually, but not always, associated with high serum drug levels.[13] Precipitating factors include hypertension, hypomagnesemia, aluminum overload, and the concomitant administration of high-dose corticosteroids. Seizures may also occur in the setting of PRES.

Peripheral nervous system complications are far less common in the setting of calcineurin inhibitors. Sensory disturbances consisting of paresthesias or dysesthesias of the distal extremities are more common than weakness. Patients may present with acute or subacute demyelinating neuropathies mimicking Guillain–Barré syndrome or chronic inflammatory demyelinating polyneuropathy (CIDP), but axonal neuropathies also occur.[13] Additionally, a calcineurin inhibitor-induced length-dependent painful neuropathy syndrome may develop in some patients with normal nerve conduction studies. Necrotizing myopathies have also been described in the setting of these medications. The treatment for all the direct neurotoxic side effects of calcineurin inhibitors is either to decrease the dose or to eliminate the drug entirely, if possible. All of these complications typically resolve with cessation of the offending agent.

Mammalian Target of Rapamycin Inhibitors

Sirolimus and everolimus are drugs that act by inhibiting the mammalian target of rapamycin (mTOR)

TABLE 44-2 ■ Noninfectious Neurologic Complications Associated With Commonly Used Immunosuppressive Medications

Immunosuppressant	Neurologic Adverse Effect
Calcineurin Inhibitors	
Cyclosporine Tacrolimus	Headache Tremor Posterior reversible encephalopathy syndrome Seizures Akinetic mutism Optic neuropathy Central pontine myelinolysis Demyelinating polyneuropathy Sensorineural hearing loss (tacrolimus)
Mammalian Target of Rapamycin (mTOR) Inhibitors	
Sirolimus Everolimus	Tremor Encephalopathy Posterior reversible encephalopathy syndrome (rare)
Antimetabolites (DNA synthesis inhibitors)	
Azathioprine Mycophenolate mofetil	Myalgias Seizures (rare; azathioprine) Headache (mycophenolate mofetil) Tremor (mycophenolate mofetil)
Monoclonal Antibodies	
Alemtuzumab Rituximab Muromonab-CD3	Headache Intracerebral hemorrhage (alemtuzumab) Ischemic stroke (alemtuzumab) Cervical artery dissection (alemtuzumab) Chemical meningitis (rituximab; muromonab-CD3) Seizures (rare; muromonab-CD3) Post-transplant lymphoproliferative disorder (muromonab-CD3)
Other	
Corticosteroids	Mania Tremor Seizures Headache Idiopathic intracranial hypertension Myopathy
Methotrexate	Chemical meningitis Encephalopathy Acute transverse myelopathy (intrathecal administration)
Cyclophosphamide	Encephalopathy
Intravenous immunoglobulin	Chemical meningitis Thromboembolism

and ultimately blocking the response of T- and B-cell activation by cytokines. Although these agents are sometimes used in a primary immunosuppressive regimen, they are commonly preferred as a milder alternative when one of the calcineurin inhibitors is not tolerated.[13] These medications each have similar side effects and cause increases in serum cholesterol and triglycerides. Myelosuppression is also common as are dermatologic complications. Although mTOR inhibitors have relatively few neurologic side effects, a PRES-like syndrome which resolves on discontinuation of the drug has been reported on rare occasion.[13]

Corticosteroids

Corticosteroids were the first immunosuppressive agents used in transplantation and continue to be used for long-term immunosuppression and for the treatment of acute graft rejection. Corticosteroids affect both cellular and humoral immunity and expose patients to a greater risk of opportunistic infection than do the newer immunosuppressive agents that are relatively T-cell specific. The most common neurologic side effects of corticosteroids are myopathy, steroid psychosis, and problems resulting from corticosteroid withdrawal.

The exact frequency of corticosteroid myopathy is unknown, but many patients taking moderate-dose corticosteroids develop some signs of myopathy 2 to 3 weeks after the start of therapy. The syndrome is characterized by proximal muscle weakness that is most severe in the hip girdle muscles. Muscle enzymes including creatine kinase are typically not elevated and electrodiagnostic testing may be normal. Muscle biopsy classically demonstrates selective atrophy of type IIA fibers. Treatment is to discontinue the corticosteroids if possible or to change to a nonfluorinated corticosteroid such as hydrocortisone. The myopathy usually resolves completely after corticosteroid therapy is stopped, but this may take months.

Another more rare diagnostic consideration in a patient taking chronic corticosteroids and presenting with weakness is spinal cord or cauda equina compression from epidural lipomatosis. This syndrome usually does not occur in patients taking less than the equivalent of 30 mg/day of prednisone. Clinical manifestations can include back pain, myelopathy, and radiculopathy. The usual treatment is surgical decompression, although simply discontinuing corticosteroid therapy occasionally leads to improved symptoms.

Psychiatric complications occur frequently in patients taking corticosteroids. The phrase *steroid psychosis* refers to several psychiatric syndromes that are associated with corticosteroids including anxiety, insomnia, irritability, difficulties with concentration and memory, and mood changes. More severe acute psychiatric syndromes are rare but include schizophrenia-like disorders and an agitated delirium. The treatment of steroid psychosis involves stopping the medication, reducing the dose, and switching to dexamethasone, the corticosteroid least likely to cause steroid psychosis. Affective syndromes may respond to lithium, whereas schizophrenia-like syndromes are treatable with psychotropic medications.

Withdrawal from corticosteroids also may cause neurologic complications, including myalgias and arthralgias ("steroid pseudorheumatism"). Also observed is a nonspecific syndrome consisting of headache, lethargy, and nausea, with or without a low-grade fever.

OKT3 Monoclonal Antibody

OKT3 (Muromonab-CD3) is a monoclonal antibody directed against $CD3^+$ lymphocytes.[13] Its major neurologic side effect is a chemical meningitis, which occurs in about 5 percent of patients during the first 3 days of exposure. CSF analysis demonstrates a lymphocytic pleocytosis with normal glucose and normal or slightly elevated protein concentration. The syndrome is self-limited and benign. Lumbar puncture and culture of the CSF should be performed to exclude bacterial or fungal meningitis. The meningeal inflammation is probably part of a cytokine release syndrome (CRS) or an allergic process similar to that which occurs with nonsteroidal anti-inflammatory drugs or intravenous immunoglobulin.

A more severe syndrome with variable degrees of altered mental status, including seizures, may occur rarely. It is associated with neuroimaging evidence of cerebral edema, but it is also self-limited and benign, even sometimes if the OKT3 is continued. OKT3 use also predisposes patients to develop PTLD, a side effect that appears to be dose related. Due to these adverse events, newer monoclonal antibodies have replaced this agent in many transplant programs.

Azathioprine

Azathioprine is an antimetabolite that suppresses both cell-mediated and humoral immunity. Although currently used less frequently in the transplant setting now that more specific immunosuppressants are available, the drug is still occasionally used for long-term immunosuppression. Very rare neurologic side effects occur including mylagias and seizures, but the nervous system may be affected secondary to opportunistic infection or liver failure caused by the medication.[13]

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) decreases the immune response by inhibiting purine synthesis in lymphocytes. Similar to azathioprine, it has no severe adverse neurologic side effects but can sometimes cause headache and myalgias.[13] Since MMF has few systemic side effects it is often a favored immunosuppressive agent.

Disease-Modifying Therapies for Multiple Sclerosis

The therapeutic landscape in multiple sclerosis (MS) has evolved significantly over the last decade with the advent of new more potent and effective agents. Though the enhanced therapeutic arsenal offers MS patients improved disease control, these new disease-modifying therapies (DMTs) come with an increased risk of adverse effects. Opportunistic infections remain amongst the most serious of these side effects and their prompt recognition is critical to successful management. PML, although uncommon, results in significant morbidity and mortality and has been reported with several DMTs, most notably with natalizumab where the probability of developing PML ranges from 1/100 to 1/10,000. The risk-assessment algorithm is based on three principal risk factors: anti-JCV antibody titer, duration of natalizumab therapy, and prior exposure to immunosuppression. Apart from natalizumab, PML has been described in association with fingolimod, dimethylfumarate, and alemtuzumab as well as with teriflunomide and ocrelizumab after transition from natalizumab. Of note, prompt discontinuation of DMT can be associated with significant rebound of MS disease activity with the potential for accrual of new deficits. Several other opportunistic infections and neurologic complications may occur in the setting of DMT use, as outlined in Table 44-3.

TABLE 44-3 ■ Noninfectious Neurologic Complications Associated With Disease-Modifying Therapies for Multiple Sclerosis

Medication	Neurologic Adverse Effect
Alemtuzumab	Headache Cytokine release syndrome Intracerebral hemorrhage Ischemic stroke Cervical artery dissection Peripheral nervous system and central nervous system autoimmune disorders
Cladribine	Headache Peripheral neuropathy
Fingolimod	Posterior reversible encephalopathy syndrome Intracerebral plasmacytic lymphoproliferative disorder
Interferons	Headache Transient worsening of prior multiple sclerosis symptoms Polyneuropathy
Natalizumab	Headache Central nervous system lymphoma
Ocrelizumab	Headache
Teriflunomide	Headache Peripheral neuropathy

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) are a novel class of therapeutic agents that have revolutionized the treatment of previously incurable malignancies. These monoclonal antibodies have been engineered to target one of two T-cell proteins, programmed cell death receptor-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and exploit the immune system's natural response to foreign targets. Under normal conditions, these checkpoints guard against autoimmunity by downregulating the immune system and suppressing T-cell activity; ICIs provide an iatrogenic blockade of these intrinsic regulators of immune homeostasis, redirecting the attack against foreign cancer cells.

Although antibodies inhibiting PD-1 and CTLA-4 have resulted in a significant survival advantage, they are associated with a variety of immune-related adverse events (irAEs), of which neurologic irAEs are among the most devastating.[14] A diverse spectrum of neurologic complications involving both the central and peripheral nervous system have been described and can occur after only a few cycles of treatment. Peripheral nervous system toxicity is more common and includes disorders involving nerve roots, peripheral nerves, neuromuscular junction, and muscle, although CNS involvement including cases of encephalitis, transverse myelitis, and cerebellitis has also been documented.

Given the novelty of ICIs, the spectrum of irAEs complicating their use continues to expand. To date, no specific clinical or biologic markers exist to predict which patients will develop side effects. There is some speculation that the presence of irAEs in a given patient might be associated with an increased efficacy of neoplasm response. Given the autoimmune nature of these complications, a genetic component is strongly suspected, and large genome-wide association studies are underway to further evaluate this question. As is the case in other autoimmune diseases, the role of the gut microbiome and other environmental factors may also be relevant.

Though neurotoxicity is uncommon, likely occurring in less than 3 percent of patients on ICIs, prompt recognition and management of irAEs is critical as observational data suggest more favorable patient outcomes with early treatment. Treatment of irAEs typically involves discontinuation of ICI, high-dose corticosteroids, and consideration of additional immunosuppressive agents including intravenous immunoglobulin or plasmapheresis.[14] In cases of significant neurologic disability, more chronic immunosuppression is sometimes necessary and consideration of a monoclonal antibody or an antimetabolite agent such as azathioprine or MMF is warranted.[14]

Chimeric Antigen Receptor T-cell Therapy

Advances in cancer immunotherapy have also led to the development of reprogrammed autologous T cells engineered to express a given chimeric antigen receptor (CAR) designated for a specific tumor target antigen. These CAR-T cells are multiplied in vitro and reinfused into patients where they reorient the host's immune response toward malignant cells, resulting in pronounced cytotoxic effects. CAR-T therapy may lead to significant side effects, including most commonly, a systemic inflammatory response caused by cytokine release from infused CAR-T cells and other host immune cells. Symptoms range from mild fever to multiorgan failure. Grading CRS is imperative in determining appropriate management and depends on four principal factors: presence of fever, hypotension, hypoxia, and evidence of organ toxicity.[15] Neurotoxicity, sometimes termed immune effector cell-associated neurotoxicity syndrome (ICANS), is now considered a distinct entity and consists of a spectrum of manifestations including altered mental status, cortical signs, seizures and increased intracranial pressure.[15] ICANS may occur in conjunction with CRS or shortly thereafter, and symptoms may progress over hours to days.

Management of patients with ICANS involves supportive care with close observation in an intensive care unit in conjunction with investigations which might include MRI and CSF studies. EEG is indicated to rule out alternative etiologies as well as continued electrographic seizures. Management of high-grade toxicity with corticosteroids and anti-interleukin-6 therapy such as tocilizumab is likely helpful.

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CHAPTER

45

Fungal Infections of the Central Nervous System

JOHN R. PERFECT

PATHOGENS

HOST FACTORS

  Immune Reconstitution Inflammatory Syndrome

CRYPTOCOCCUS NEOFORMANS* AND *GATTII

COCCIDIOIDES IMMITIS* AND *POSADASII

HISTOPLASMA CAPSULATUM

BLASTOMYCES DERMATITIDIS

PARACOCCIDIOIDES BRASILIENSIS

SPOROTHRIX SCHENCKII

TALAROMYCES MARNEFFEI

***CANDIDA* SPECIES**

***ASPERGILLUS* SPECIES**

MUCORMYCOSIS

***SCEDOSPORIUM* SPECIES**

PHAEOHYPHOMYCOSIS

HYALOHYPHOMYCOSIS

DIAGNOSIS

TREATMENT

  Specific Fungal Infections in the Central Nervous System

    Cryptococcal Meningitis

    Candida *Meningitis*

    Coccidioidal Meningitis

    Other Fungal Infections

  Surgical Treatment

Recognition of fungal infections of the central nervous system (CNS) is increasing in frequency due to the growing population of immunocompromised patients and improvements in diagnostic techniques. Published information on the diagnosis and treatment of these diverse infections ranges from extensive to nonexistent. Therefore, a comprehensive survey of the literature coupled with clinical experience informs the diagnosis, pathophysiology, and management of these potentially life-threatening infections. Major recent references are cited here, and earlier comprehensive references can be found in previous editions of this book.

PATHOGENS

Fungi that cause CNS infection can be divided into two general groups. The first group consists of primary pathogens including *Cryptococcus neoformans/gattii*, *Coccidioides immitis/posadasii*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Histoplasma capsulatum*, *Talaromyces marneffei*, *Pseudallescheria boydii* (*Scedosporium apiospermum*), and the dematiaceous molds. CNS involvement by these fungi can occur in patients with apparently intact immune systems and, at even higher rates, in immunosuppressed patients. The second group consists of secondary opportunists that cause CNS infection almost exclusively in patients with defective host defenses; this group includes *Candida* species, *Aspergillus* species, and mucormycosis caused by fungi in the order Mucorales. Finally, some fungi for which only a few case reports of CNS involvement exist are mostly common in the environment and include *Alternaria*, *Rhodotorula*, *Aureobasidium*, *Arthrographis*, *Acremonium*, *Clavispora*, *Blastoschizomyces*, *Trichosporon*, *Sepedonium*, *Bipolaris*, *Schizophyllum*, *Paecilomyces*, *Pneumocystis*, and *Ustilago*. Such cases generally have some unique feature in the medical history, such as direct trauma or CNS penetration, that explains the presence of the fungus in the CNS. Two prime examples are the fungal meningitis outbreaks of 2002 with *Exophiala* (Wangiella) *dermatitidis* and of 2012 with *Exserohilum rostratum*; both were associated with injection of compounded, preservative-free corticosteroids.

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Some of the key characteristics of the more common CNS fungal infections are listed in Table 45-1.

HOST FACTORS

Geographic factors are important for certain CNS fungal infections. Several groups of fungi are not geographically restricted and have worldwide distribution including *Candida albicans* and other *Candida* species, *Aspergillus* species, and *C. neoformans/ C. gattii*. However, other mycoses such as histoplasmosis, blastomycosis, coccidioidomycosis, talaromycosis (penicillinosis), and paracoccidioidomycosis are largely confined to certain geographic areas, although these lines are blurred with modern travel. It is therefore essential that clinicians evaluating patients with possible fungal infections acquire an accurate travel history.

The CNS is an immunologically sequestered site, with anatomic barriers that exclude not only invading microorganisms but also some components of the immune system. Host defenses normally are highly effective in excluding fungi from the CNS, but certain conditions can lead to failure of these protective functions. Some of these conditions are obvious, such as trauma or the presence of indwelling catheters that allow direct inoculation of fungi into the CNS, immaturity of the blood–brain barrier in neonates, and a high-grade fungemia. In most cases, the fungus enters via the respiratory tract and seeds the CNS hematogenously, but other extracranial origins of CNS infection have been identified such as abscesses, mycotic aneurysms, and meningitis, which can arise from septic emboli associated with endocarditis. Rhinocerebral mucormycosis involves both vascular invasion and direct neural sheath extension into the CNS.

The most important risk factor for the development of CNS fungal infections is suppression of the host immune system, whether due to an underlying disease or to immunosuppressive drugs. Both the etiology of these CNS infections and their responses to therapy depend on the type of immune suppression. For instance, administration of immunosuppressive drugs such as systemic corticosteroids is a leading risk factor for development of CNS fungal infections with *C. neoformans/gattii* and *Aspergillus* species. Neutropenia due to cancer chemotherapy is associated with CNS infections caused by *Aspergillus* and *Candida* species, and treatment with the iron chelator deferoxamine predisposes to rhinocerebral mucormycosis. Several specific underlying diseases

TABLE 45-1 ■ Features of Common Fungal Infections of the Central Nervous System

				Major Pathologic Manifestations		
Pathogen	**Risk Factors**	**CSF Cultures Positive**	**CSF Serologies**	**Meningitis**	**Infarct**	**Abscess or Mass**
Aspergillus spp.	Neutropenia, corticosteroids	Rare	None	+	++++	++
Blastomyces dermatitidis	None known	Rare	Ab	+	–	++
Candida spp.	Neutropenia, corticosteroids, CSF shunts, polymorphonuclear leukocyte defects, prematurity	50%	None	++	–	+++
Coccidioides immitis	AIDS, corticosteroids	25–45%	Ab	++++	+	+
Cryptococcus neoformans	AIDS, corticosteroids	75–85%	An	++++	+	++
Dematiaceous fungi	None	Rare	None	+	–	++++
Histoplasma capsulatum	AIDS, corticosteroids	50%	Ab/An	+++	+	+
Paracoccidioides brasiliensis	None	Rare	None	++	–	+
Scedosporium species	Corticosteroids, aspiration	Rare	None	++	–	++
Sporothrix schenckii	Alcohol, AIDS?	Rare	Ab	++	–	–
Zygomycetes (Mucorales)	Diabetes, deferoxamine, intravenous drug use	Rare	None	+	++++	+++

Ab, antibody test; An, antigen test; AIDS, acquired immunodeficiency syndrome; CSF, cerebrospinal fluid.

are associated with an increased incidence of CNS fungal infections. For instance, the most important of these associations is the link between the acquired immunodeficiency syndrome (AIDS) and cryptococcal meningitis. Prior to the advent of antiretroviral therapy (ART), rates reported from several cities ranged between 24 and 66 per 1,000 AIDS patients in the United States, but this incidence has been reduced with effective ART. Cryptococcal meningitis continues to occur early, in some patients who have either not received or have stopped antiretroviral drugs, or later, as viral resistance develops to ART. In 2009, the US Centers for Disease Control estimated that worldwide there were 1 million cases per year of cryptococcosis, with over 600,000 deaths, which made it the most deadly invasive fungal infection in the world. With widespread ART availability, the yearly incidence has now been estimated at 270,000, with 180,000 deaths. Cryptococcal meningitis accounts for approximately 8 percent of all invasive mycoses among transplant recipients. There have also been several reports of patients infected with human immunodeficiency virus (HIV) who have contracted CNS infections with *Aspergillus* species and the use of high-dose ibrutinib for cancer therapy has been associated with *Aspergillus* and cryptococcal CNS infections.[1,2] Mold infections have been manifested predominantly as cerebral mass lesions, although cerebral infarctions, meningitis, and spinal cord involvement have also been observed. Patients with advanced HIV infection may also present with disseminated and CNS histoplasmosis, talaromycosis, coccidioidomycosis, blastomycosis, or sporotrichosis.

Patients who undergo organ transplantation and receive concomitant immunosuppression are at a significant risk of CNS fungal infection. The most common fungal pathogens in this setting are *C. neoformans*/*C. gattii*, *Aspergillus* species, and *Candida* species. Infection with *C. neoformans* in organ transplant recipients is usually manifested as a chronic or subacute meningitis occurring 6 months or more after organ transplantation. Infections with *Aspergillus* and *Candida* species usually occur within the first 2 months after organ transplantation, and CNS involvement is usually manifested by brain abscesses. CNS aspergillosis may be underdiagnosed in organ transplant recipients; in one series of 44 brains from liver transplant recipients examined at autopsy, 9 cases of cerebral aspergillosis were identified, of which only 2 were diagnosed before death.

Other high-risk underlying diseases or conditions associated with CNS fungal infection include malignancies, diabetes mellitus, and prematurity. Poorly controlled diabetic patients with or without ketoacidosis are at increased risk of rhinocerebral mucormycosis. Premature infants are at risk of disseminated infections and specifically of meningoencephalitis with *Candida* species, which has substantial implications for survival and for neurodevelopment issues with CNS involvement.

Infections that arise from direct inoculation of fungi into the CNS are usually seen after head trauma or neurosurgical procedures or as complications of implanted cerebrospinal fluid (CSF) shunts. In patients who have open head injuries, fungi that are ubiquitous in the environment may contaminate the wounds, leading to meningitis and focal fungal brain abscesses. With CSF leaks, the initial infection may be bacterial, but during the use of prolonged broad-spectrum antibacterial drugs, superinfection with *Candida* can occur.

CNS fungal infections can be associated occasionally with the presence of a CSF-diverting shunt. The most common fungus associated with CSF shunt infections is *C. albicans*. It appears that infection occurs as a result of either contamination of the shunt apparatus during insertion or subsequent manipulation, or through hematogenous spread. Among the published cases of CSF shunt infections with *C. albicans*, an association exists with recent antibacterial therapy and colonization with *Candida* species at other body sites. Other fungi that have caused CNS infection in the setting of a CSF shunt include *C. neoformans*, *Trichosporon beigelii*, *Candida glabrata*, and *Candida tropicalis*. There is some controversy concerning the origin of cryptococcal shunt infections. In many of the patients with CSF shunts who were subsequently found to have *C. neoformans* infection, the shunts were originally placed for either idiopathic hydrocephalus or chronic culture-negative meningitis; these patients probably had chronic CNS cryptococcal infection before their shunts were inserted.

There are rare reports of fungal infection associated with neurosurgical procedures; among these, *Aspergillus* and *Candida* species account for most cases. In some of these patients, infection was attributed to direct extension of the fungus from the paranasal sinuses, and in others it was thought that fungi were introduced with devices inserted during the operative procedure. Many of these patients have additional predisposing conditions such as prior treatment with antibacterial agents or high-dose corticosteroids. The dramatic outbreak of over 500 patients with meningitis, arachnoiditis, and epidural abscesses due to *E. rostratum* contamination of injectable corticosteroids around the spine emphasizes how fungi can aggressively establish disease. They travel through tissue after direct inoculation and are helped by immunosuppression, such as with corticosteroids.

Immune Reconstitution Inflammatory Syndrome

While some host immunity is critical for the eradication of CNS infections, immunologic recovery can also be detrimental and contribute toward worsening disease expression. This entity of overstimulation of the immune system has been called *immune reconstitution syndrome* or *immune reconstitution inflammatory syndrome* (IRIS) and has been described vividly during ART, in transplant recipients with immunosuppressive drug manipulations, and even in apparently normal hosts with cryptococcal meningitis. For example, upon initiation of ART during management of HIV-related cryptococcal meningitis, HIV RNA levels decline rapidly and there is repopulation of the host with memory and naïve $CD4^+$ lymphocytes; within 4 to 6 weeks, an immunologic shift occurs from a Th2 to a Th1 immune response. IRIS may be manifested by headaches, fever, CSF lymphocytosis, increased intracranial pressure, and evidence of increased inflammation on neuroimaging without evidence of viable yeasts in the CSF. In IRIS the cryptococcal CSF polymerase chain reaction (PCR) is generally negative, but it remains positive if viable CSF yeasts are present, indicating infection relapse or persistent infection before return of culture results.[3] The pathologic finding in tissue is that of granuloma formation. Patients who initiated ART within 2 weeks of treatment for *C. neoformans* CNS infection are significantly more likely to develop IRIS and have a worse outcome than those who initiated ART at a later time. This observation has led to controversy about when precisely to start ART during the management of cryptococcal meningitis—present guidelines give a generous range of between 2 and 10 weeks for ART initiation after the start of antifungal therapy and most clinicians start ART at 4 to 5 weeks.

Similarly, in solid organ transplant recipients with cryptococcosis, IRIS was observed in 5 percent of patients within 1 to 2 months after initiation of antifungal therapy and was more common in those receiving potent immunosuppressive regimens and those with graft loss. IRIS occurs in patients in whom there is a rapid shift in immune reactivity. Since the appearance of IRIS in fungal CNS infections is commonly misconstrued as a treatment failure or relapse of infection that leads to unwarranted or inappropriate changes in specific therapy, its clinical recognition is extremely important. IRIS should be considered when treatment appears to have controlled the fungal disease by culture or biomarker data but new signs of inflammation develop symptomatically or on imaging studies.

Recognition of IRIS is important to the clinical management of CNS fungal infections because overabundance of inflammation can lead to clinical worsening. Thus, corticosteroid therapy for IRIS may be considered to reduce inflammation and cerebral edema.

CRYPTOCOCCUS NEOFORMANS AND GATTII

The encapsulated yeast *C. neoformans* is the most common cause of fungal meningitis worldwide. The first report of cryptococcal infection in humans was provided by Busse and Buschke in 1894 in a patient with bone infection and probable disseminated disease. The first case of meningeal cryptococcal infection was reported 10 years later, in 1905, and cryptococcosis emerged as a significant CNS infection during the twentieth century. The number of infections with *C. neoformans* rose dramatically in the United States and certain African countries following the onset of the AIDS epidemic. It peaked at approximately a million cases per year, but even with the advent of widespread ART it is estimated that there are approximately 270,000 cases per year, with over 180,000 deaths.[4]

This ubiquitous encapsulated saprophytic yeast occupies a wide environmental niche. It is found worldwide in bird excreta, soil, animals, and even humans. A large outbreak of *C. gattii* infections in the Pacific Northwest was associated with trees. It is likely that most infections occur after inhalation of small yeasts or basidiospores, leading to a primary pneumonia or a primary lung–lymph node complex in which the yeasts remain dormant for long periods in the host, until the host defenses become weakened. The reason that this yeast has a particular tendency to spread to the CNS remains imprecisely explained. It is likely that *Cryptococcus* travels by three mechanisms across the blood–brain or blood–CSF barrier: (1) transcytosis; (2) paracellular; and (3) the Trojan Horse method. Ligands on *C. neoformans* such as the hyaluronic acid antigen (CPS1) have been associated with the CD44 receptor on brain endothelial cells, perhaps allowing for transcytosis through the blood–brain barrier. Another cryptococcal mechanism for transcytosis is to use the secreted yeast metalloprotease encoded by the *MPR1* gene. On the paracellular front, the *UREl* gene and its encoded protein help control trafficking of the yeast directly through the blood–brain barrier. Finally, multiple experiments have shown *Cryptococcus* to travel across the blood–brain barrier within mononuclear cells (Trojan Horse effect). It is anticipated that not only are there multiple mechanisms for CNS targeting but that many cryptococcal genes are involved in the efficient movement of *Cryptococcus* into the brain.

CNS infection usually manifests as a meningitis or meningoencephalitis, although mass lesions or torulomas may be seen. There are four serotypes (A to D) based on the type of capsular polysaccharide, which are then divided into several species: *C. neoformans* var. *grubii* or *neoformans* (serotypes A and D), and *C. gattii* (serotypes B and C). Furthermore, *C. neoformans* has been divided into multiple genotypes or subspecies of VNI, VNII, VNB (I and II), VNIII, and VNIV; *C. gattii* has been divided into five cryptic species (VGI–V). All serotypes can cause meningitis, but there is some geographic variation in their distribution for disease; for example, most patients with cryptococcal meningitis in the United States and Europe have been infected with either the serotype A or D strains. Infections with *C. gattii* are found more commonly in southern California, Southeast Asia, and Australia; this distribution reflects the natural distribution of certain *Eucalyptus* trees that are likely one of the environmental yeast repositories. A recent outbreak of *C. gattii* infections on Vancouver Island showed that there are other trees, such as firs and oaks, that can contain this fungus, perhaps related to ecologic evolution in the setting of global climate change. Despite earlier reports that many patients with cryptococcal meningitis had no known immune deficiency, recent experience suggests that a much higher proportion of patients have some identifiable form of immunosuppression. About 10 percent of patients with cryptococcal meningitis have no known underlying disease but a series of host-altered genes linked with an increased genetic susceptibility to cryptococcosis have been identified.[5] However, most cases occur in those with known defective cell-mediated immunity due to corticosteroid treatment, reticuloendothelial malignancy, organ transplantation, sarcoidosis, collagen vascular diseases, or AIDS. Use of new anticancer agents such as ibrutinib (kinase inhibitor) can be associated with rapid development of cryptococcal and *Aspergillus* brain infections. Lymphocyte functions are abnormal in most patients with disseminated cryptococcosis. Patients with HIV infection have severe lymphocytopenia with CD4 counts below 100/μL. Most patients with AIDS and cryptococcal meningitis present with a particularly high burden of CSF yeasts. India ink examinations of the CSF are positive in over 80 percent of patients, and extraordinarily high titers of cryptococcal polysaccharide antigen in CSF and serum are common, with quantitative viable CSF yeast counts that can exceed 10^6 colony-forming units (CFU)/mL of CSF. The response of some of these patients to infection includes a paucity of CSF leukocytes; approximately two-thirds of patients with AIDS and cryptococcal meningitis have fewer than 20 leukocytes/mm^3 in their CSF on presentation. This combination of a high burden of yeasts and a quantitative deficiency in the inflammatory response indicates an impaired immune system and can lead to a poor prognosis despite administration of fungicidal therapy.

Patients with cryptococcal meningitis may present with a wide spectrum of CNS findings, ranging from symptoms of headaches with or without fever to subacute dementia developing over months. The latex agglutination test and enzyme-linked immunosorbent assay are both sensitive ($>90\%$) and specific ($>90\%$) if proper controls are used. An inexpensive and simple lateral flow assay (LFA) has been developed and it compares favorably to the other antigen tests.

The recent addition of the BioFire PCR Film Assay uses multiplex PCR for major CNS pathogens and includes *C. neoformans.* Two aspects to this test need to be discussed. First, false negatives occur with low burden of yeasts, so pelleting CSF before PCR testing may be necessary. Second, a positive PCR test supports the fact that viable yeasts are present and might be used in deciding between relapse of infection and IRIS. Although cases occasionally are difficult to diagnose, with the proper use of CSF culture, India ink studies, polysaccharide antigen, and PCR tests, the only limiting factor in the diagnosis of CNS cryptococcosis is usually failure to perform a lumbar puncture because the diagnosis is not considered.

COCCIDIOIDES IMMITIS AND *POSADASII*

C. immitis and *C. posadasii* are dimorphic fungi with a natural habitat in semiarid soil, which explains their geographic distribution in the southwestern United States and in parts of Mexico and South America. Because many tourists travel through these areas and may become infected, clinicians outside the organism's natural habitat occasionally encounter coccidioidomycosis. Inhalation of the arthrospores leads to a primary pulmonary infection. Most patients remain asymptomatic, and fewer than 0.2 percent of primary infections disseminate outside the lung. Occasionally, the fungus reaches the meninges, either by hematogenous spread or direct extension from osteomyelitis of the skull or vertebrae; seeding of the CNS usually occurs a few months after the primary infection.

Symptoms of chronic meningitis are most common. There are cases in which brain involvement occurs without meningitis, but this presentation is unusual. Spinal arachnoiditis with obstructive hydrocephalus and cerebral vasculitis with infarcts and abscesses also have been reported. It appears that patients with coccidioidomycosis involving the facial skin are at higher risk of meningitis than those with skin involvement at more distant body sites.

Diagnosis may be confirmed by culture of the fungus from the CSF, but in endemic areas it is diagnosed in many patients on the basis of a CSF pleocytosis (which demonstrates eosinophilia in up to 70% of cases) and the presence of complement-fixing antibodies (CFAs) in the CSF. CFA titers are positive in approximately 70 percent of patients at initial diagnosis, and in almost all patients as meningitis progresses. A new *Coccidioides* antigen test of CSF can also frequently detect CNS involvement.[6,7]

It is likely that genetic susceptibility plays an important role as a risk factor for meningitis. For instance, meningitis appears to develop at greater rates in Blacks, Filipinos, and possibly other ethnic groups such as Hispanics compared to Whites.

Most patients who contract CNS infection with *Coccidioides* have no apparent underlying disease, but immunosuppressed patients are at greater risk of CNS involvement after primary infection. Corticosteroid treatment has been associated with more severe manifestations of primary infection, as well as with reactivation of latent disease and dissemination to the CNS. There have also been many reported cases of CNS infection with *Coccidioides* in patients with AIDS and in transplant recipients. The natural history of coccidioidal meningitis is such that patients whose only detected extrapulmonary site of infection is the CNS live significantly longer than those with more diffuse disease. White blood cell count in the CSF decreases during the course of both treated and untreated infection, and therefore cannot be used to gauge response to therapy. Unfortunately, lifelong triazole therapy for meningitis is required because of the extremely high rate of relapse after initial induction antifungal therapy.

HISTOPLASMA CAPSULATUM

H. capsulatum is a dimorphic fungus endemic in certain areas of the Ohio and central Mississippi River Valley in the United States as well as in Latin America. It can be found in bird and bat guano, and in soil contaminated with this guano. Outbreaks of the disease have been attributed to disturbance of contaminated soil, allowing the conidia to become airborne and inhaled. Asymptomatic infection in endemic areas is very common; skin test data indicate that up to 69 percent of the population show evidence of prior infection in certain endemic areas. Most infected individuals have minimal symptoms, and dissemination occurs only rarely. When dissemination does occur, between 10 and 25 percent of patients develop CNS involvement. Although granulomas and other brain parenchymal lesions have been described, most patients with CNS lesions present with meningitis.

Although *Histoplasma* meningitis can occur in apparently normal hosts, it occurs in immunocompromised populations at a higher rate. Patients with AIDS, solid organ transplant recipients, and those receiving biologics such as anti-TNF therapy are at high risk of development of disseminated disease, usually due to reactivation of latent infection. Because CSF cultures may be positive in only 10 to 30 percent of cases even when large volumes (10 to 20 ml) of CSF are incubated for weeks, it is important to use CSF serologies. There are occasional serologic cross-reactions with other fungi, which can cause diagnostic confusion. However, the *Histoplasma* CSF polysaccharide antigen has been found to be positive in 40 percent of patients with *Histoplasma* meningitis and is a reasonable first screening test for this fungus in the CNS.

BLASTOMYCES DERMATITIDIS

B. dermatitidis and recently discovered *Blastomyces helicus* are dimorphic fungi endemic in Africa and in certain parts of the lower Mississippi River Valley, North Central states, and mid-Atlantic states in the continental United States. It is presumed that spores are inhaled from a source in the soil, but its natural location in the environment has been identified only occasionally. Most individuals have subclinical disease, and dissemination occurs rarely. Disseminated blastomycosis is characterized by granulomatous and suppurating lesions of the lung, bone, and skin. In some series, blastomycosis has been reported to involve the brain in 6 to 33 percent of disseminated cases. Although patients with CNS blastomycosis usually present with evidence of infection at other sites, occasionally meningitis is the initial presentation and there is no evidence of extraneural disease. CSF cultures are rarely positive, and a chronic neutrophilic pleocytosis is a common finding in blastomycotic meningitis. In cases of subacute and chronic meningitis, screening the CSF by *Blastomyces* antigen testing may be helpful, although the sensitivity and specificity of such testing are not well characterized.

CNS involvement occasionally presents with a mass lesion (blastomycoma) within the brain parenchyma.

Immunocompromised patients are at increased risk of disseminated infection with *B. dermatitidis*. A review of 24 cases of infection with *B. dermatitidis* in a heterogeneous population of immunocompromised patients showed 6 cases of disseminated disease, including 4 with CNS involvement.

PARACOCCIDIOIDES BRASILIENSIS

P. brasiliensis is a dimorphic fungus endemic to subtropical areas of Mexico and Central and South America. The lung is the primary location for initial infection; a few patients present with widely disseminated disease that can involve the CNS. Small case series report dissemination in 9 to 27 percent of patients, and the infection reportedly involves the CNS in approximately 13 percent of cases with disseminated disease.

Meningitis is an unusual manifestation of CNS infection with *P. brasiliensis*, with brain parenchymal involvement more common; patients frequently present with seizures. CNS infection occurs in normal hosts and in those who are immunosuppressed. The host response against this microorganism remains poorly understood but an immunosuppressed individual probably has an increased chance of CNS involvement.

SPOROTHRIX SCHENCKII

S. schenckii and its other species are worldwide saprophytes of vegetation, notably sphagnum moss. Sporothricosis presents as a chronic infection of the skin and the subcutaneous lymphatic system, developing after a primary inoculation such as a rose-thorn puncture or cat scratch. Pulmonary disease from inhalation of spores is uncommon. Dissemination beyond the skin, lung, and joints is rare; only approximately a dozen cases of *Sporothrix* meningitis have been reported in the literature, and most do not have overt extraneural disease at presentation. Diagnosis of this infection with its low fungal burden in the CNS can be extremely difficult using traditional culture methods. To reduce diagnostic delays of up to 6 to 7 months, a test for *Sporothrix* antibodies in the CSF should be performed; it may be the only clue to the diagnosis.

Although meningitis with *S. schenckii* is so uncommon that risk factors cannot be defined accurately, certain patients may be predisposed to dissemination from a local infection including patients with myelodysplastic syndromes, ethanol abusers, or patients taking corticosteroids. Disseminated and CNS sporotrichosis has also been described in patients with AIDS.

TALAROMYCES MARNEFFEI

Talaromyces (Penicillium) marneffei is a dimorphic fungus that is found in the geographic range of bamboo rats, and has become a common cause of opportunistic infection in HIV-infected patients in certain parts of Southeast Asia and China. Pathophysiologically, the infection appears similar to histoplasmosis but it has a unique predisposition for producing skin lesions, and blood cultures are usually positive. In one series, 3 of 20 CSF samples were positive for this fungus during disseminated disease. Importantly, around 10 percent of patients with disseminated talaromycosis may also have a concomitant cryptococcal meningitis.

CANDIDA SPECIES

Candida species form part of the normal human microbial flora and rarely cause invasive disease unless host defenses are impaired. The yeast can gain access to the blood stream and then the CNS via contaminated intravenous catheters or through illicit intravenous drug use. Neonates, neutropenic patients, and those recovering from major surgery are particularly susceptible to invasive candidiasis, including CNS involvement. However, neutropenic patients rarely have CNS involvement despite a high incidence of bacteremia and fungemia. The placement of foreign bodies in the CNS, such as drug wafer implants and shunts, can also provide an entry for *Candida* infections. Based on autopsy studies, *Candida* species are the most common fungi to invade the CNS in the setting of malignancy, and their ability to transverse the immature blood–brain barrier efficiently is a dreaded complication of fungemia in neonates with both mortality and associated neurodevelopmental morbidity. *Candida* may cause meningitis, ventriculitis, or brain parenchymal lesions such as abscesses or granulomas. *C. albicans* is the species implicated in most CNS *Candida* infections, but other species such as *C. tropicalis*, *Candida lusitaniae*, and *Candida parapsilosis* will occasionally produce CNS disease.

In the normal host, *Candida* rarely causes deep-seated infections. Factors that can encourage spread of *Candida* from mucosal surfaces to deeper tissues, such as the subarachnoid space, include prematurity, broad-spectrum antibacterial therapy, hyperalimentation, malignancy, indwelling catheters, treatment with corticosteroids, neutropenia, abdominal surgery, diabetes mellitus, burns, and intravenous drug use. *Candida* invades brain tissue more commonly than the subarachnoid space.

Candida meningitis has been reported in both congenital and acquired immunodeficiency syndromes, emphasizing the importance of the host response. For example, patients with chronic granulomatous disease of childhood and myeloperoxidase deficiency may present with *Candida* meningitis. Several cases of *Candida* meningitis have been reported in patients with the global immune defects caused by severe combined immune deficiency and the specific innate immunity defects of chronic mucocutaneous candidiasis. Furthermore, specific gene nucleotide polymorphisms in innate immune genes such as *CARD9* are described as risk factors for *Candida* meningitis. Therefore, a specific underlying immune deficiency should be considered in any case of spontaneously occurring *Candida* meningitis, especially in children. Patients with AIDS frequently have mucocutaneous forms of candidiasis such as thrush and esophagitis, but involvement of the CNS has been reported rarely in these patients. *Candida* meningitis has been described as a superinfection of the CNS in patients recovering from bacterial meningitis. *Candida* infection can involve the brain and subarachnoid space by direct extension through trauma, ventriculostomy placement, ventricular shunts, or after other neurosurgical procedures, particularly in the presence of antibacterial use. *Candida* uncommonly can also invade from the adjacent paranasal sinuses or bone. Intracranial extension of the infection may occur through an arteritis and can even lead to subarachnoid hemorrhage.

The CSF in *Candida* meningitis can show a predominance of either mononuclear or neutrophilic cells. Only half of routine CSF cultures yield the fungus, despite the fact that *Candida* organisms are easy to grow in the laboratory; a large CSF volume is needed to optimize culture because of low fungal burden, and better methods of CSF detection need to be validated to detect *Candida* products such as arabinitol or antigens such as β-D-glucan or mannan. The clinical significance of a positive culture for *Candida* from CSF obtained through an indwelling device such as a ventriculostomy tube may not be clear as the fungus is a frequent contaminant; if a positive culture is found and CSF parameters are normal, another CSF specimen should be obtained from a separate lumbar puncture. In the absence of symptoms or an abnormal CSF profile, and with a negative follow-up culture, further treatment is probably unnecessary but the device should be removed and, when necessary, replaced.

ASPERGILLUS SPECIES

Aspergillus species are ubiquitous in the environment and can be found in the air of most buildings, including hospitals. Both neutrophils and macrophages provide important host defense mechanisms directed against the spores and hyphae of *Aspergillus*. CNS infection with *Aspergillus* species can develop by direct extension from the paranasal sinuses, by direct inoculation after head trauma, following surgery, or by hematogenous spread in immunocompromised hosts, particularly those with prolonged neutropenia. This fungus accounts for approximately 5 percent of CNS fungal infections. A clinically important characteristic of *Aspergillus* infections is their angioinvasive attack on arteries, causing thromboses and cerebral infarction or mycotic aneurysm. Less commonly, meningitis and meningoencephalitis can occur, and rhinocerebral disease similar to mucormycosis has been described.

Most intracranial infections with *Aspergillus* occur in neutropenic patients. The risk of disseminated aspergillosis with subsequent brain parenchymal involvement or meningitis increases with the duration of neutropenia. Individuals receiving high doses of ibrutinib for CNS lymphomas are at high risk for CNS aspergillosis. Most infections manifest as brain parenchymal lesions, but spinal cord lesions may also develop. Occasionally, *Aspergillus* infection involves the vertebrae and eventually the subarachnoid space. Patients with chronic granulomatous disease of childhood with its lack of an oxidative burst by phagocytes are particularly susceptible to this type of infection. The pulmonary alveolar macrophage may be most important in initial control of this ubiquitous fungus in the lungs, but polymorphonuclear leukocytes are probably crucial in defense against CNS invasion.

Diagnosis can be delayed because of insensitivity of cultures, and both a CSF PCR and galactomannan antigen tests on CSF are helpful in diagnosing CNS involvement.

MUCORMYCOSIS

Fungi of the order Mucorales are widespread in the environment and infection is usually due to inhalation of spores. The genus *Rhizopus* is responsible for most human infections. CNS infection in immunocompromised hosts can occur by direct extension from the paranasal sinuses, through hematogenous spread such as with illicit intravenous drug use, or by spread along nerve roots. Mucormycosis commonly is associated with angioinvasion of arteries with thrombosis and resulting tissue infarction. Presentation involving invasion of the subarachnoid space occurs occasionally, but disease limited to the meninges is unusual. In a large review of 929 cases with mucormycosis, 283 patients had CNS infection, of which 69 percent were rhinocerebral, 16 percent were localized cerebral infection, and 15 percent had hematogenous dissemination from other organs.

Patients with diabetes mellitus (with or without ketoacidosis) or malignancy, and those receiving immunosuppressive drugs or prolonged voriconazole therapy are at risk for this invasive mold infection. There have been reports of disseminated mucormycosis, including brain involvement, in patients on dialysis receiving the iron chelator, deferoxamine; this agent may interfere with the antifungal activity of transferrin, thus allowing for dissemination of the mold. A different iron chelator, deferasirox, cannot be used as a siderophore by the fungus and actually has been evaluated as a treatment of mucormycosis as it competes for essential iron supplies with the fungus.

SCEDOSPORIUM SPECIES

Scedosporium species have a worldwide distribution in soil and contaminated water. These fungi are being renamed and have been known as *P. boydii*, *Monosporium apiospermum*, or *S. apiospermum* when in the asexual state. Although rare, CNS infection with these molds can result in brain abscesses or chronic neutrophilic meningitis. Classically, CNS infection is associated with aspiration of contaminated water during trauma, or near-drowning in fresh water. Presumably, the fungus penetrates through the cribiform plate during water immersion or establishes a pulmonary focus with later dissemination to the CNS, producing meningitis or brain abscesses. Other risk factors for infection include corticosteroid use and diabetes.

PHAEOHYPHOMYCOSIS

The dematiaceous fungi are a group of common environmental molds that have brown pigment in their walls; diverse genera are linked by their ability to produce melanin. This group of fungi has occasionally caused CNS infection, and for certain species it appears that there is some neurotropism. For instance, *Cladosporium trichoides*, also known as *Xylohypha bantiana* and finally renamed as *Cladophialophora bantianum*, is the most common isolate of this class of fungi found in CNS infections, which usually manifest as a brain abscess, although meningitis has been described. Meningitis and brain abscesses caused by other species of these "black molds" are also occasionally reported, such as with *Rhinocladiella mackenzei* in the Middle East.

CNS infections with these organisms have been caused by contaminated corticosteroid injections around the spine. In 2002, *E. dermatitidis* produced four cases of meningitis from contaminated corticosteroids injected epidurally for pain management. Patients presented with headaches, altered mental states, and focal neurologic findings approximately 1 to 3 months after the injections. A larger outbreak of *E. rostratum* infections in 2012 and 2013 involved over 500 cases; clinical presentations ranged from meningitis with or without stroke to parameningeal infections (e.g., epidural abscess, arachnoiditis with cauda equina syndrome, and vertebral osteomyelitis).[8]

Many patients diagnosed with brain abscesses due to one of these dematiaceous fungi have no apparent underlying immune defect, but immunosuppressed patients may be at special risk. The portal of entry for these fungi is not known in most cases, but because of a predilection for abscess formation in the frontal and parietal lobes, at least some of these infections may result from direct extension through the sinuses.

HYALOHYPHOMYCOSIS

Nonpigmented, hyaline filamentous molds cause occasional infections of the CNS. For instance, meningitis and cerebritis have been reported with *Acremonium* and *Paecilomyces* species. In severely neutropenic patients, the soil saprophytes, *Fusarium* species, can produce CNS lesions. Because of similar histopathologic features, *Fusarium* infection can be confused with aspergillosis unless cultures are performed or histopathologic tissue specimens have PCR and sequencing performed on them. In the growing immunosuppressed population, *Trichosporon* infection, which usually involves only superficial skin or hair shafts, can disseminate to the brain; CNS infections with *T. beigelii* or *T. ashaii* and *Blastoschizomyces capitatus* (*Saprochaete capitatum*) have been reported to cause CNS diseases.

DIAGNOSIS

The specific diagnosis of CNS fungal disease can be very challenging, even in the setting of known disseminated fungal infections. Factors that lead to this difficulty include the unusual and varied clinical presentations of patients with CNS fungal infections, difficulty in culturing organisms from the CNS due to a low burden of fungus, and the lack of sensitive serologic tests for many fungi.

Even in cases of cerebral mass lesions due to fungi, patients may present with nonfocal neurologic symptoms and signs. For instance, many patients present only with altered sensorium or seizures, despite having extensive CNS infection on neuroimaging. Fungal meningitis usually leads to chronic signs and symptoms including a combination of fever, headache, lethargy, confusion, nausea, vomiting, stiff neck, and neurologic deficits. However, the characteristic markers of CNS infection, fever and headache, both may be absent, and patients may present initially only with a subacute dementia. Cases of cryptococcal, coccidioidal, and *Histoplasma* meningitis may be indolent, with symptoms persisting for months to years if untreated; in consequence, the timing of symptoms is not always an accurate guide to diagnosis. In contrast, occasional cases of cryptococcal meningitis present acutely after only several days of symptoms, especially in severely immunocompromised patients and particularly those receiving ibrutinib or high doses of corticosteroids, or with advanced HIV infection.

Fungal infection is a primary consideration in the differential diagnosis of patients with chronic meningitis, defined as those with meningitis-related CNS abnormalities that either progress or fail to improve during at least 4 weeks of observation. The differential diagnosis of chronic meningitis includes both infectious and noninfectious causes (Table 45-2) but fungal infection should be high in the differential diagnosis. It may also be particularly difficult to distinguish infection due to fungi from that caused by certain other subacute or chronic CNS pathogens such as mycobacteria.

TABLE 45-2 ■ Differential Diagnosis of Chronic Meningitis

Infectious Causes	Noninfectious Causes
Fungal infections	Chronic benign lymphocytic meningitis
Mycobacterial infections	Subarachnoid hemorrhage
Parameningeal infections	Systemic lupus erythematosus
Syphilis	Granulomatous arteritis
Lyme disease	Carcinomatous meningitis
Brucellosis	Sarcoidosis
Toxoplasmosis	Behçet disease
Nocardiosis	
Actinomycosis	
Leptospirosis	
Helminthic meningitis	
Viral meningitis	

The CSF findings in fungal meningitis are well described. In most instances a mononuclear pleocytosis is present, with leukocyte counts ranging between 20 and 500 cells/mm^3. In some cases of fungal meningitis there is a predominance of polymorphonuclear cells. Eosinophilic pleocytosis of the CSF has been described in approximately 70 percent of cases of coccidioidal meningitis and, rarely, in cases of cryptococcal meningitis. Very low CSF leukocyte counts ($<10/\text{mm}^3$) may occur when patients are severely immunosuppressed; a normal CSF profile has even been observed in some cases. CSF protein levels usually are elevated, but if very high protein concentrations (≥ 1.0 g/dL) are present, a subarachnoid block should be considered. CSF glucose concentrations may vary from normal to low. The causes of hypoglycorrhachia are listed in Table 45-3. The finding of a low glucose concentration in the CSF favors an infectious disorder and may have prognostic significance in that persistent hypoglycorrhachia after treatment for cryptococcal meningitis without HIV infection raises concern for risk of relapse. Elevated CSF pressures of 250 mm CSF or higher may have prognostic and therapeutic implications, particularly in cryptococcal meningitis.

It is unusual to see fungi on direct stains prepared from CSF, except in the case of cryptococcal meningitis. The India ink test is not commonly used now that a rapid, cheap, and accurate antigen test is available. India ink preparations of CSF are positive in only 50 percent of all patients with cryptococcal meningitis, and in 80 percent or more of those who have underlying HIV infection. The number of fungi present in CSF in cases of fungal meningitis is highly variable. In some cases of cryptococcal meningitis, there are at least 10^6 CFU/mL of CSF, whereas the dimorphic fungi often have less than 1 CFU/mL of CSF. Approximately 75 percent of all patients with cryptococcal meningitis yield positive CSF cultures; patients with HIV infection have positive cultures in more than 90 percent of cases. Unfortunately, in meningitis cases due to fungi other than cryptococci, CSF cultures are often negative, and

TABLE 45-3 ■ Differential Diagnosis of Low Cerebrospinal Fluid Glucose Concentration

Acute bacterial meningitis
Mycobacterial meningitis
Fungal meningitis
Subarachnoid hemorrhage
Carcinomatous meningitis
Meningeal cysticercosis/trichinosis
Drug-induced meningitis (nonsteroidal anti-inflammatory agents)
Acute syphilitic meningitis
Chemical meningitis (direct intrathecal injections)
Viral meningitis (rare)
Hypoglycemia
Rheumatoid meningitis
Lupus myelopathy
Amebic meningitis

they are rarely positive in patients with cerebral mass lesions. For example, only one-third to one-half of patients with coccidioidal meningitis yield CSF cultures that are positive. Patients with blastomycotic meningitis rarely yield positive CSF cultures, and in proven *Histoplasma* meningitis it is difficult to find the organisms in the subarachnoid space, even at necropsy. Because the burden of organisms in CSF is so often low, relatively large volumes of CSF (10 to 20 ml) should be obtained and sent for culture in suspected cases.

The laboratory should centrifuge specimens and culture the sediment on appropriate fungal media. *Candida* organisms usually can be identified within a few days; in occasional patients, hypertonic media may be helpful for growing the yeast. In neonates, CSF cultures are important as blood cultures may be negative and CSF parameters may be normal in culture-positive *Candida* meningitis. *Cryptococcus* should be identified within 3 to 10 days in most cases, but the classic dimorphic fungi (e.g., *Histoplasma* or *Coccidioides*) may require longer incubations. The lysis-centrifugation method for isolating *H. capsulatum* from blood and CSF has improved detection compared with routine methods. Blood cultures may also be helpful for identifying the fungus that is causing meningitis in a particular host; *Candida* species, *Talaromyces*, or *Cryptococcus* are the fungi most likely to be present on blood cultures. CSF cultures can also be negative simply because the samples were not taken from the localized site of active infection. For example, because fungi commonly cause a basilar meningitis, cisternal or ventricular fluid may occasionally yield organisms when fluid from the lumbar space is sterile.

Serologic tests are important for the diagnosis of many fungal infections in the CNS. For example, the latex agglutination test, ELISA, and LFA[9] for detection of cryptococcal polysaccharide antigen are the best serologic tests for this pathogen and can be used with rapidity on blood, serum, or CSF. The tests can be positive even when culture is negative. When samples are heated to eliminate rheumatoid factor and proper controls for nonspecific agglutination and interfering substances are used, the antigen tests are more than 90 percent sensitive and specific for cryptococcal infection. If surface condensation from agar plates is added to the assay, false-positive results may occur, which can also be seen with disseminated *T. beigelii* infections and paravertebral bacterial infections. If a positive antigen test occurs in a patient whose clinical presentation is not consistent with cryptococcal meningitis, the laboratory should repeat the test, and if it is still positive, a repeat lumbar puncture is indicated. False-negative results may be due to very low burdens of pathogens, a prozone phenomenon due to antigen excess, or the performance characteristics of various different proprietary antigen detection kits. The value of using cryptococcal antigen titers as a general prognostic guide is well established; however, following serial titers are less valuable for guiding specific therapeutic decisions.

With the availability of an accurate and cheap LFA, in areas of high incidence of cryptococcal disease, screening for serum cryptococcal antigen can be undertaken in new cases of documented HIV infection with low CD4 counts.[10] Positive serum cryptococcal antigen titers will initiate a lumbar puncture to rule out CNS disease. If culture and antigen are negative in CSF and serum titer is low (≤1:256), preemptive fluconazole treatment may be started until ART improves immunity.

Detection of the *Histoplasma* polysaccharide antigen in urine and serum is a valuable adjunctive test in the diagnosis of disseminated disease. It is also useful in monitoring therapy and for the early detection of relapsing infection in HIV-positive patients. False-positive results may occur in patients with meningitis due to other fungi. Tests detecting CSF antibodies against *Histoplasma* antigens are also useful, and are positive in approximately 75 percent of patients with CNS infection. Although sensitive, these antibody tests are not highly specific, and positive results may also be found in patients with other fungal infections or with bacterial meningitis. The best way to diagnose CNS *Histoplasma* infections when cultures are negative is to perform both antigen and antibody testing on the CSF. Empiric treatment for *Histoplasma* infection should be started in patients with chronic meningitis of uncertain etiology when the antigen or antibody assays are positive in the CSF.

In coccidioidomycosis, elevated serum CFA titers above 1:32 to 1:64 are the hallmark of disseminated disease. Some patients with isolated meningitis without extraneural infection may also have low serum CFA titers. In patients with coccidioidal meningitis, CFA titers are present in the CSF in 70 percent of patients initially and in almost 100 percent as the infection progresses. A coccidioidal antigen test is now available and may be helpful. CFA is absent from unconcentrated CSF in the presence of high-serum titers due to extraneural disease, unless there is a parameningeal lesion next to the dura. The CFA titers appear to parallel the course of meningeal disease and have been used to guide treatment; titers should decline with successful therapy.

The ability to detect specific antibodies in CSF has been used in the diagnosis of meningitis caused by *S. schenckii*. Waiting for culture data can lead to delays of up to 7 months from the onset of symptoms, and therefore latex agglutination and enzyme immunoassay tests have been used successfully to detect CSF antibodies confirming the diagnosis of *Sporothrix* meningitis. When a titer cut-off of 1:8 or higher is used, there is no cross-reaction with other fungal, bacterial, or viral pathogens.

There is intense interest in developing serologic tests for other fungal infections, especially those due to *Candida* and *Aspergillus*. Detection of unique antigens (β-D-glucan and mannan) or metabolic products (arabinitol and mannitol) from these fungi in CSF has not yet been extensively validated in the clinical setting of meningitis. However, β-D-glucan is frequently detected in CSF with many fungal CNS infections and may be a good screen.[11] Furthermore, the galactomannan and β-D-glucan detection tests for *Aspergillus* in the CSF are likely to be useful in diagnosing and managing this rare and difficult-to-detect infection.[12,13]

Two other approaches for diagnosis of fungal meningitis are detection of host products and the use of molecular amplification. Although not specific for fungi, CSF lactic acid concentrations usually are elevated in fungal meningitis and, in some cases, specific fungal T-cell responses can be detected. It is likely that as further experience accumulates with PCR-based diagnostics for meningitis, fungal sequences will be included in new diagnostic approaches. For example, *C. neoformans* is part of the BioFire Film Array CNS panel that uses PCR. As previously noted with cryptococcal PCR, a false negativity may occur with a low burden of yeasts in the CSF, and CSF may thus need to be centrifuged prior to testing. The approach may be helpful in distinguishing IRIS from relapse since a positive PCR likely means that there are viable yeasts in CSF. For difficult-to-diagnose fungal infections, whole-genome sequencing of CSF may eventually become useful to detect and identify fungal DNA in the CSF.

Imaging studies can be helpful in the diagnosis and staging of CNS fungal infections. Localization of mass lesions or areas of leptomeningeal inflammation by computed tomography (CT) or magnetic resonance imaging (MRI) can guide the neurosurgeon to areas for biopsy. MRI with contrast enhancement is more sensitive than contrast CT scans. In cases of fungal meningitis, CT and MRI may be unremarkable or show leptomeningeal enhancement, hydrocephalus, infarction (as with mucormycosis), or edema. During treatment, there may be slow resolution of CNS lesions on imaging studies despite effective treatment, and clinicians must take this into account. When meningitis is refractory to conventional diagnostic approaches, meningeal biopsy for histologic study and culture can be considered, although false negatives can occur.

TREATMENT

Experience in the treatment of fungal CNS infections is varied. For example, treatment for cryptococcal meningitis has been studied extensively, whereas many fungal CNS infections are so rare that only a few cases have been described. An important adjunct to antifungal therapy is the reversal, if possible, of any immunocompromising conditions. This may include decreasing doses of corticosteroids or the use of immunomodulators to improve host immunity. However, CNS infections require very close monitoring when host immunity is changed.

Specific Fungal Infections in the Central Nervous System

CRYPTOCOCCAL MENINGITIS

Before the availability of amphotericin B, cryptococcal meningitis was uniformly fatal, although occasionally an untreated patient survived for several years. Early treatment trials showed that immunosuppressed patients with cryptococcal meningitis had higher treatment failure rates than immunocompetent patients. Patients with AIDS were found to have low response rates to initial therapy and high relapse rates once therapy was stopped. Because of this important dichotomy in the patient populations with cryptococcal meningitis, the treatments for patients with and without HIV infection are discussed separately. The 2010 Cryptococcal Guidelines of the Infectious Diseases Society of America (IDSA) separated risk groups into those with AIDS, transplant recipients, and non-AIDS, nontransplant patients.

Nonimmunosuppressed Patients

Amphotericin B used alone at daily doses of 0.4 to 0.8 mg/kg per day for 10 weeks provides effective therapy for patients without HIV infection who develop cryptococcal meningitis. The addition of flucytosine to this regimen has been studied in an effort to decrease both the duration of therapy and the total dose of amphotericin B. Following early trial data, experience with amphotericin B plus flucytosine as primary therapy in cryptococcal meningitis has accumulated. This combination usually sterilizes the CSF within 2 weeks and cures many patients within 4 to 6 weeks, with manageable amphotericin B toxicity. Patients with good prognostic features and no known immunosuppressive conditions have been successfully managed with as little as 4 weeks of combined therapy. The regimen nevertheless requires the administration of an intravenous medication for prolonged periods, and some treatment failures (15 to 30%) do occur.

Treatment regimens using oral antifungal agents for cryptococcal meningitis would obviously be attractive, and therefore both itraconazole and fluconazole have been tried. There are no large trials comparing azole antifungals with amphotericin B in patients without HIV infection. Personal experience and data extrapolated from trials in patients with AIDS suggest that high-dose fluconazole can be used successfully as monotherapy for patients with cryptococcal meningitis, but is not as effective as the combination of amphotericin B plus flucytosine because of reduced fungicidal activity. Therefore, most experts do not recommend use of fluconazole (1200 mg/day) alone for induction therapy of cryptococcal meningitis. Itraconazole has also been used successfully in treating cryptococcal meningitis, but because there is more experience with fluconazole, many physicians consider this the preferred azole. A compromise can be reached in an effort to reduce the amount of time on intravenous therapy by using an induction phase of amphotericin B plus flucytosine followed by prolonged consolidation and maintenance (suppressive) phases with oral fluconazole.

This combined drug regimen is highly recommended in treatment guidelines published by the Infectious Diseases Society of America, and consists of amphotericin B at a dose of 0.7 to 1.0 mg/kg per day plus flucytosine at a dose of 100 mg/kg per day to keep serum levels below 100 μg/mL for 2 weeks, after which the patient is switched to fluconazole at a dose of 400 to 800 mg/day, assuming normal renal function, for a minimum of 10 weeks. There has been a substantial clinical switch to using AmBisome 3 to 4 mg/kg per day rather than conventional amphotericin B so there is less toxicity and thus less interruption of therapy, which may be important for success. A lumbar puncture should also be considered after 2 weeks; if the CSF PCR or culture still yields *C. neoformans*, treatment with amphotericin B (AmBisome) and flucytosine should be reinstituted for another 2-week course of induction therapy. If the CSF is sterile after induction amphotericin B plus flucytosine therapy, fluconazole can be started. The total duration of fluconazole therapy should be tailored to the individual patient, but at least 10 weeks of treatment should be administered. Because most relapses of cryptococcal meningitis occur within 6 months to 1 year after stopping therapy, generally a maintenance or suppressive dose of fluconazole 200 to 400 mg/day is given for 6 months to 1 year in patients who do not have HIV infection. Additional and higher doses of fluconazole may be required in patients with brain parenchymal lesions, persistent symptoms, concomitant immunosuppressive therapy, or underlying immunosuppressing diseases. Patients with torulomas may require longer induction therapy.

The need for intraventricular or intrathecal amphotericin B in cryptococcal meningitis remains controversial. Some investigators have used intraventricular amphotericin B with success in cases with a poor prognosis. However, this route of administration is rarely necessary and may have complications. In high-risk patients, it may be better to switch to lipid-based amphotericin B regimens and use doses up to 5 or 6 mg/kg per day, or possibly higher, rather than risk the side effects of direct injection of amphotericin B into CSF. These lipid formulations are highly recommended in transplant recipients and generally for all patients to avoid drug interruption.

Once therapy has been started, the frequency of lumbar punctures should be determined by clinical response. As mentioned earlier, a lumbar puncture performed after the second week of therapy should show that the CSF is sterile, particularly if the combination of amphotericin B and flucytosine was used. Once therapy is completed, further lumbar punctures should be considered depending on the patient's signs and symptoms. Persistently elevated polysaccharide antigen titers or positive India ink examinations indicate failure of therapy only when the CSF culture is positive or the patient demonstrates neurologic deterioration. There is probably little value in following serial cryptococcal polysaccharide antigen titers acutely to make therapeutic decisions.

Immunosuppressed Patients

The management of cryptococcal meningitis in patients with AIDS presents a major therapeutic challenge. Response to initial therapy in ART-treated cases has improved, and the relapse rate, which was once very high, has been reduced by maintenance or suppressive fluconazole treatment and ART. Recurrence of symptomatic cryptococcal meningitis in patients with AIDS is typically due to the same strain that caused the original infection and it is thought that the prostate or brain parenchyma can serve as sites for persistent residual infection despite sterilization of the CSF.

There is a substantial amount of clinical data to support recommendations for the treatment of AIDS-associated cryptococcal meningitis published by the Infectious Diseases Society of America. Induction therapy includes amphotericin B 0.7 to 1.0 mg/kg per day with flucytosine 100 mg/kg per day for 2 weeks. The combination regimen is favored because of more rapid CSF sterilization, potentially fewer relapses, and better outcomes.[14] In patients who have significant renal dysfunction, liposomal amphotericin B 3 to 4 mg/kg per day or amphotericin B lipid complex 5 mg/kg per day can be substituted for conventional amphotericin B. The induction period usually lasts for 2 weeks but can vary depending on clinical response. Patients are then switched to fluconazole (400 to 800 mg/day) for 10 weeks. Fluconazole alone has been evaluated for primary therapy of cryptococcal meningitis, but clinical experience suggests that it takes longer to sterilize the CSF than amphotericin B and requires higher doses. If given orally for induction, fluconazole should be given with flucytosine. Triazoles may be more effective when the burden of yeasts in CSF is lower. It is anticipated that 80 to 90 percent of patients will respond well to this initial combination course of therapy.

In resource-limited areas the availability, safety, and cost of polyene therapy for 2 weeks can be problematic. In such circumstances, a combination of amphotericin B plus flucytosine for 1 week has been shown to be effective.[15] The use of one dose of AmBisome (10 mg/kg) on a fluconazole base is also successful.[16] Thus, depending on healthcare resources, induction therapy may vary, but these abbreviated short-course polyene strategies should not be used at present in resource-available healthcare systems. An unresolved issue is that in Africa flucytosine is not available consistently.

The third stage of the treatment plan is the continued use of fluconazole at a dose of 200 mg/day for prevention of relapses. The high rate of relapse in these patients led to the initial institution of lifelong fluconazole suppressive therapy for all patients with AIDS who respond to initial treatment for cryptococcal meningitis. However, the immune restoration associated with ART has prompted reinvestigation of lifelong suppression; patients who have been treated with ART and have a sustained immunologic response may be able to safely discontinue maintenance therapy. Appropriate candidates for stopping maintenance therapy are patients who have had at least 1 year of therapy with fluconazole, along with a CD4 count above 100 cells/μL (or more than 10% CD4 cells). These patients should be monitored closely, and fluconazole maintenance reinstituted if the CD4 count falls below 100 cells/μL or below 10 percent CD4 cells or if there is reappearance of serum cryptococcal antigen titers that were previously negative. In one prospective trial, 42 patients who had responded to antifungal therapy for cryptococcal meningitis were randomized to either continue or discontinue maintenance therapy for cryptococcal meningitis once the CD4 count had increased to above 100 cells/μL and the HIV viral load had been below 50 copies/mL for 3 months on ART; over a median follow-up of 48 weeks, no relapses occurred in either group. It is important to note that ART should not be started during the first 2 weeks of induction therapy for cryptococcal meningitis because of higher mortality.[17] ART is generally delayed for 5 to 6 weeks after the start of cryptococcal therapy.

Complications

Increased intracranial pressure is a well-described problem in patients being treated for cryptococcal meningitis. Symptoms in such patients usually begin shortly after initiating antifungal therapy and include systemic hypertension, increasing headaches, impaired consciousness, visual impairment, cranial nerve palsies, and death. These symptoms can occur suddenly, and head imaging usually shows no evidence of hydrocephalus or mass lesions. The opening pressure at lumbar puncture can be extremely high (≥250 mm of CSF). The pathophysiologic cause of increased intracranial pressure in this setting is uncertain but may well be CSF outflow obstruction. Most patients with AIDS-associated cryptococcal meningitis present with increased intracranial pressure, and up to 70 percent of this patient population will have opening pressures exceeding 200 mm of CSF on the initial lumbar puncture. In these patients, symptoms generally respond rapidly to removal of large volumes of CSF, which can be accomplished with CSF drainage.[18] Treatment guidelines published by the Infectious Diseases Society of America recommend that sufficient CSF be removed to achieve a closing pressure either below 200 mm of CSF or 50 percent of the opening pressure. Some patients require serial lumbar punctures for relief of severe symptoms and physical findings; for those patients requiring very frequent lumbar punctures, placement of a ventricular shunt should be considered. Despite theoretical concerns regarding placement of catheters into infected spinal fluid, experience shows no increased difficulties in clearing the infection if effective antifungal therapy has already been started. Placement of a lumbar drain is an option, but the relatively frequent complication of bacterial superinfection precludes long-term use. The use of corticosteroids or acetazolamide to decrease raised intracranial pressures in the setting of AIDS-associated cryptococcal meningitis does not appear to be beneficial except when corticosteroids are used in the setting of IRIS. Indeed, the routine use of corticosteroids is not beneficial in cryptococcal meningitis,[19] unlike for tuberculous meningitis.

Visual loss in cryptococcal meningitis may not respond to maneuvers aimed at decreasing intracranial pressure. Blindness is usually not due to endophthalmitis, is often bilateral, and may be permanent. Many treatments have been tried with inconsistent results in an effort to restore vision including repeated lumbar punctures, treatment with corticosteroids, fenestration of the optic nerve sheath, and release of perioptic nerve arachnoidal adhesions.

The management of IRIS in cyptococcal meningitis is not precise. First, the diagnosis is clinical but is considered when CSF cultures and PCR are negative and the antigen is stable or decreasing on therapy despite persistent or increasing evidence of inflammation by CSF analysis or neuroimaging. Treatment is not well studied but, importantly, clinical response does occur to corticosteroids,[20] but dose and duration remain empiric.

There are several major prognostic factors that determine the outcome of patients with cryptococcal meningitis. Control of the underlying disease is the most important factor. The burden of yeasts in the CSF, indicated by positive India ink examinations, high polysaccharide antigen titers, and elevated intracranial pressure, is also predictive. High numbers of yeasts worsen the prognosis, and patients may then need more aggressive individual clinical management. The impact of the host response is also important; patients with a poor CSF inflammatory response, such as those with less than 20 leukocytes/mm^3 on CSF examination, do not respond as well to therapy, and studies suggest that immunomodulators may be of help. Interferon-gamma levels in the CSF may help determine clearance of infection, and treatment with recombinant interferon-gamma with antifungal agents tends to reduce CSF yeast counts faster than antifungal agents alone. However, immune modulators are not standard therapy because of IRIS and lack of immune stimulation precision. Finally, symptoms at presentation, such as a decreased sensorium, suggest advanced disease and also a poor prognosis.

CANDIDA *MENINGITIS*

While there are reports of spontaneous cures of meningitis due to *Candida* species, clinical experience suggests that treatment is indicated for all patients. Even with treatment, mortality rates for *Candida* meningitis range between 10 and 20 percent. There is no consensus on the best regimen, but the combination of amphotericin B and flucytosine has synergistic activity against *Candida* in vitro and has resulted in a high-cure rate. There is substantial experience with amphotericin B alone, which also can successfully treat *Candida* meningitis. Fluconazole with its high CSF penetration can be used in certain cases, although it usually does not sterilize CSF as fast as amphotericin B—containing regimens. Liposomal amphotericin B has been used after failure of conventional amphotericin B and has been combined successfully with flucytosine. In patients with ventriculoperitoneal shunts or ventriculostomies, it is recommended that any prosthetic material or device be replaced during systemic antifungal therapy. Although mortality has improved with treatment, neurodevelopmental disabilities may persist in neonates. Echinocandins have poor CNS penetration and therefore have not been favored in treatment of *Candida* meningitis.

COCCIDIOIDAL MENINGITIS

In contrast to meningitis due to other fungi, the primary mode of treatment for coccidioidal meningitis with amphotericin B is not systemic but intraventricular. In these infections, systemic amphotericin B in a total dose of 0.5 to 1.0 g is given mainly to treat undetected foci outside the CNS and lipid formulations probably could be substituted with higher-dose exposure. Control of the CNS infection is then achieved by intraventricular administration of amphotericin B. Intrathecal therapy is begun with small doses of 0.01 mg/day and increased gradually, as tolerated, up to 0.5 mg/day. The drug can be administered into the lumbar, cisternal, or ventricular space; the latter is preferred. Arachnoiditis, neurotoxicity, and secondary bacterial infections of the CSF can complicate therapy. Recommendations for length of therapy are variable, and because of the poor prognosis for complete cure some patients have been treated indefinitely. The CSF leukocyte count has been used to follow progress and to judge the need for further therapy. Lowering of the CSF antibody titers after treatment is a good prognostic sign. If the patient worsens during treatment, the possibility of hydrocephalus or a superimposed bacterial infection should be considered.

There has been some clinical benefit from treatment with oral azoles. Miconazole and ketoconazole have been tried, but response has been only fair, and therefore these agents are not recommended. More experience has focused on using fluconazole and itraconazole as therapy for coccidioidal meningitis. In one study of 47 patients with coccidioidal meningitis treated with fluconazole 400 mg/day, a positive response to therapy occurred in 37 patients unrelated to the presence of hydrocephalus or HIV infection. Toxicity is minimal in patients treated for long periods. It is therefore reasonable to consider fluconazole as a first-line agent in patients with coccidioidal meningitis; its ease of administration and lack of toxicity compared with intrathecal amphotericin B are important considerations. The optimal dose of fluconazole is not certain and some authorities believe that at least 800 mg/day of fluconazole should be used as initial treatment. The use of induction therapy with intrathecal amphotericin B followed by long-term azole therapy has also been proposed as a possible treatment option in some cases. It is unclear what role voriconazole or posaconazole will have in treatment of refractory disease. Current treatment strategies consider coccidioidal meningitis to be suppressed rather than cured, thus requiring lifelong therapy. Observational studies suggest that with current treatments, over 70 percent of patients will relapse on discontinuation of treatment.

OTHER FUNGAL INFECTIONS

Meningitis due to *Histoplasma*, *Sporothrix*, or *Blastomyces* usually responds to prolonged courses of amphotericin B or lipid formulations of amphotericin B. The role of azole drugs in these infections is not clearly defined, but they are generally used only after aggressive induction treatment, most commonly with a lipid amphotericin B formulation. *Scedosporium* CNS infections may respond to initial therapy with the extended-spectrum triazoles such as voriconazole. Cotrimoxazole has been used successfully in *Paracoccidioides* meningitis. In one study *Talaromyces* infections appeared to respond better to amphotericin B than itraconazole treatment, although CNS disease was not a focus of the study.

Infections of the CNS with *Aspergillus* species generally have been fatal despite therapy. However, there are a few cases of successful therapy with high-dose amphotericin B, and extended-spectrum new triazoles such as voriconazole have improved outcome in CNS aspergillosis. Patients with CNS aspergillosis may be considered for combination therapy with voriconazole or posaconazole plus an echinocandin and possibly also the addition of lipid amphotericin B. It also may be helpful to debulk a large abscess surgically.

Mucormycosis of the CNS should be treated initially with high doses (5 mg/kg daily) of lipid formulations of amphotericin B and, if possible, surgical debridement of infarcted tissue. Surgical debulking of fungal masses is even more important in the phaeohyphomycoses, which then may be treated with a combination of a polyene, an azole, an echinocandin, and possibly flucytosine.

Surgical Treatment

Neurosurgical procedures can play an important role in the diagnosis and treatment of some CNS fungal infections. Obtaining appropriate CSF or tissue samples for diagnosis using neurosurgical procedures may be required in some cases. The placement of CSF-diverting shunts may be needed in cases of hydrocephalus or increased intracranial pressure, even during the period of active drug treatment of infection. The placement of reservoirs to allow for chronic intrathecal administration of antifungals may also be required in certain CNS infections.

Surgical resection of parenchymal lesions has been undertaken to reduce mass effect in some cases of *Histoplasma*, *Cryptococcus*, and *Aspergillus* infection, but for these fungi the presence of parenchymal CNS lesions usually does not routinely indicate the need for neurosurgical excision. In contrast, when black molds such as *Cladophialophora* or *Rhinocladiella* species and other dematiaceous fungi cause mass lesions, surgical resection or debulking is usually encouraged for cure. Rhinocerebral infections due to mucormycosis also require prompt debulking of necrotic tissue in the brain.

Fungal infections of CSF shunts and reservoirs are uncommon and are most often due to *Candida* species. Shunt infections should be treated with removal of the shunt and systemic antifungal therapy when possible. However, there are cases in which shunt removal is not possible or in which shunt placement occurs during periods of active drug treatment of meningitis. It is recommended that in the setting of a CNS fungal infection, the shunt should be removed if it was placed prior to the initiation of antifungal therapy.

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CHAPTER

46

Parasitic Infections of the Central Nervous System

ANITA A. KOSHY

PROTOZOAN INFECTIONS
- Cerebral Malaria
- Cerebral Toxoplasmosis
- African Trypanosomiasis
- Primary Amebic Meningoencephalitis and Granulomatous Amebic Encephalitis
- Cerebral Amebiasis due to *Entamoeba histolytica*

HELMINTHIC INFECTION
- Cestodes
  - *Cysticercosis*
  - *Echinococcosis (Hydatid Disease) and Sparganosis*
- Nematodes
  - *Disseminated Strongyloidiasis*
  - *Trichinosis*
  - Angiostrongylus cantonensis
  - Gnathostoma *spp.*
  - *Visceral larval migrans:* Toxocara *spp. and* Baylisascaris procyonis
  - Onchocerca volvulus *and* Loa loa
- Trematodes
  - *Schistosomiasis*
  - *Paragonimiasis*

Protozoans and helminths are responsible for a significant burden of human disease, disproportionately affecting resource-limited countries worldwide. These agents are collectively referred to as parasites, implying dependence on an adversely affected host, but in this context they are no different from other infectious agents, such as bacteria and viruses.

Protozoan parasites are single-celled, microscopic organisms that generally undergo multiplication in the mammalian host. In contrast, helminthic parasites are multicellular, vary tremendously in size, and, in general, are less capable of multiplying within the mammalian or definitive host.

Protozoa and helminths have complex life cycles and have adapted to exist within the hostile environment of one and sometimes several hosts. The distribution of these infectious agents parallels the poor socioeconomic conditions in the developing world. However, with widespread travel, infections due to these agents are being seen more frequently in nonendemic settings. In addition, with the increasing number of immunosuppressed patients resulting from infection with human immunodeficiency virus (HIV) or after transplant or chemotherapy, disease manifestations can be more frequent, severe, and aggressive. Central to the clinician's approach to the patient with a central nervous system (CNS) infection with a protozoan or helminthic organism is a thorough travel history and an increased index of suspicion. Once such an infection is suspected, an appropriate work-up can be initiated.

The protozoa and helminths that cause the bulk of CNS disease are summarized in Table 46-1.

PROTOZOAN INFECTIONS

Cerebral Malaria

Malaria is the most important parasitic infection worldwide. In 2017 an estimated 219 million cases were reported, about 90 percent of which were from Africa. About 435,000 deaths were due to malaria, with approximately 60 percent occurring in children younger than 5 years of age. While Southeast Asia continues to see steady declines in malaria cases, declines in Africa have slowed or reversed recently.[1]

Malaria infection is widely distributed (Fig. 46-1). Five species of malaria infect humans: *Plasmodium falciparum*,

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TABLE 46-1 ■ Parasitic Infections of the Central Nervous System

Organism	Geographic Distribution	Major CNS Syndromes	Mode of Infection
Protozoans			
Plasmodium falciparum	Africa, Haiti, South America, Southeast Asia, Oceania	Encephalopathy, coma, seizures	Mosquito
Toxoplasma gondii	Cosmopolitan	Congenital: retinopathy, intracranial calcification, intellectual developmental disability, seizures Immunocompromised: encephalitis, meningoencephalitis, mass lesions	Undercooked meat; contaminated water; vertical transmission
Trypanosoma brucei gambiense, *T. brucei rhodesiense*	Democratic Republic of Congo > Chad, Central African Republic (*T.b.g.*); Malawi, Uganda (*T.b.r*)	Personality changes, indifference, stupor, and coma in late stages	Tsetse flies
Naegleria fowleri	Southern United States, Australia, Great Britain, former Czechoslovakia	Acute rapidly progressive meningoencephalitis	Fresh water
Acanthamoeba spp.	Cosmopolitan	Subacute, chronic meningoencephalitis	Fresh water, soil
Balamuthia mandrillaris	Southern United States, South America	Subacute, chronic meningoencephalitis	Soil > water
Entamoeba histolytica	Africa, Mexico, South America, India, Southeast Asia	Brain abscess	Fecal–oral
Helminths			
Taenia solium	Cosmopolitan	Neurocysticercosis: seizures, hydrocephalus, chronic meningitis	Fecal–oral
Trichinella spp.	Cosmopolitan	Seizures, meningoencephalitis	Uncooked meat
Angiostrongylus cantonensis	Southeast Asia, Pacific Basin (including Hawaii)	Eosinophilic meningitis	Uncooked snails, crustacea
Gnathostoma spinigerum	Southeast Asia > Mexico, Central and South America	Eosinophilic meningitis	Uncooked fish, frog, bird, snake
Toxocara spp., *Baylisascaris procyonis*	Cosmopolitan	Seizures, palsies, retinal mass	Fecal–oral
Schistosoma species	Africa, Asia, Brazil	Seizures, cerebritis, tumor, spinal cord compression	Exposure to infected fresh water
Paragonimus species	Asia, Central and South America	Meningitis, mass lesion, infarction	Uncooked crustacea

CNS, central nervous system.

Plasmodium vivax, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*, although *P. knowlesi* is predominantly zoonotic. *P. falciparum* predominates in sub-Saharan Africa (>99% of cases), Haiti, New Guinea, Southeast Asia, South America, and Oceania. *P. vivax* predominates in the Americas and is common in endemic areas outside of Africa. Approximately 1,700 cases of malaria are diagnosed in the United States per year, primarily in recent travelers to and immigrants from areas in which malaria is endemic.

The life cycle of *Plasmodium* is similar across species. The infective sporozoites are injected by female *Anopheles* mosquitoes into subcutaneous tissue or directly into the blood stream, and thereafter circulate to the liver to invade hepatocytes. Parasites multiply, and after 1 to 2 weeks, schizonts rupture and release thousands of merozoites, which then enter the blood stream to infect erythrocytes. Of the five *Plasmodium* spp. that infect humans, *P. vivax* and *P. ovale* can establish a latent liver stage, which must be treated to avoid recrudescent infection.

Invasion of erythrocytes by merozoites requires specific surface receptors on the parasite and erythrocyte. In contrast with other *Plasmodium* species, *P. falciparum* uses multiple redundant pathways to invade, including sialic acid-dependent glycophorin pathways and nonsialic

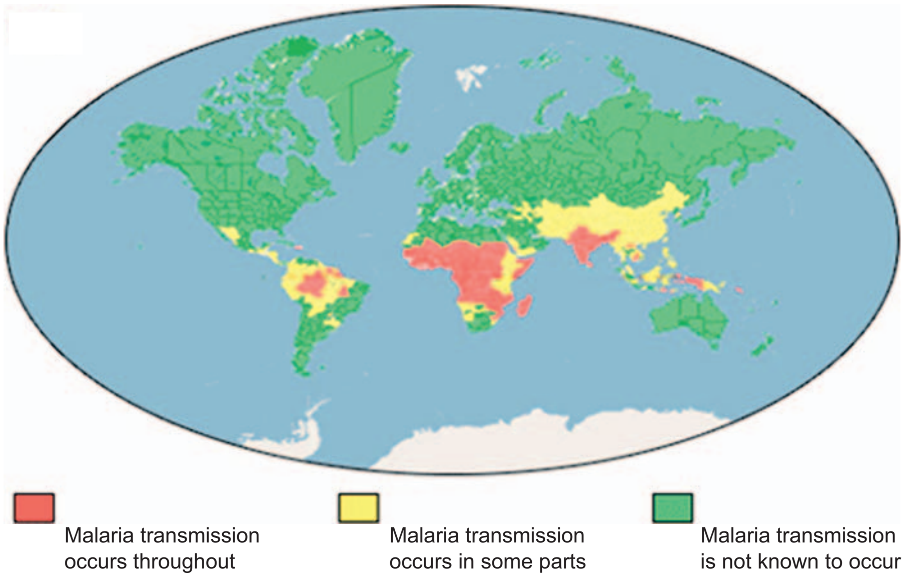
🟥 Malaria transmission occurs throughout
🟨 Malaria transmission occurs in some parts
🟩 Malaria transmission is not known to occur

FIGURE 46-1 ■ Global map of malaria transmission. (From the US Centers for Disease Control and Prevention.)

acid-dependent ones. In addition, *P. falciparum* can invade erythrocytes of all ages, and parasitemia can reach high levels. The magnitude of parasitemia was previously thought to relate to the degree of morbidity and mortality, but other factors such as the degree of metabolic stress in nutritionally deficient children, presence of parasitic coinfections, and other less-understood mechanisms may play significant roles in adverse outcomes.

Within the erythrocyte, merozoites eventually develop into schizonts, which rupture to release merozoites capable of infecting new erythrocytes. Only the asexual erythrocytic stages are directly deleterious to the host, and the mechanisms involved in the development of clinical manifestations are related to fever, anemia, and tissue hypoxia, as well as to host factors including immunopathologic events.

While high fever and rigors are the hallmarks of acute malaria, some patients with acute malaria, often those under age 5, will develop severe malaria, which is defined as having clinical or laboratory evidence of organ dysfunction (e.g., renal failure, pulmonary edema, coma). Most severe malaria, including cerebral malaria, occurs in patients with *P. falciparum*, though *P. vivax* can also cause severe malaria.

Cerebral malaria occurs in 0.5 to 1 percent of *P. falciparum* cases and is associated with a 15 to 20 percent mortality. Significant neurologic sequelae develop in around 10 percent of cases. Sequestration of parasitized erythrocytes within the capillaries of the cerebral cortex is typically observed, but is likely not the only pathogenic mechanism. While the pathogenesis of cerebral malaria is incompletely understood and remains highly speculative, it is postulated that parasitized red blood cells express parasite-derived variant surface antigens, causing the erythrocytes to adhere to endothelial cells of venules, resulting in microvascular obstruction. Specific *var* genes, the gene family that encodes the malarial cytoadherence protein *P. falciparum* erythrocyte membrane protein 1, and host receptors are postulated to play key roles in cerebral malaria pathogenesis. In addition, recent data suggest that endothelial cells are a major site of pathology as these cells show signs of activation, including characteristic morphologic changes, upregulation of surface adhesion molecules and antigens, and production of numerous cytokines and other mediators of inflammation.[2]

The World Health Organization (WHO) defines cerebral malaria as unarousable coma in a person with *P. falciparum* asexual parasitemia in whom other causes of encephalopathy have been excluded. Children under 5 have the highest rates of cerebral malaria, though adults and older children can also develop the disease. As noted earlier, it remains unclear as to what host or parasite factors determine the development of cerebral malaria. Presenting features may include seizures (15 to 20% in adults, 80% in children), disturbances of consciousness, acute delirium, meningismus, and, infrequently, focal neurologic abnormalities, including pyramidal signs, cranial nerve abnormalities, or movement disorders. Decorticate posturing or decerebrate posturing is more common in children and may indicate increased intracranial pressure or hypoglycemia. Adults are more likely than children to present with diffuse encephalopathy and no focal neurologic signs. As severe malaria affects other organs, concomitant findings can include hepatosplenomegaly, pulmonary edema, renal dysfunction, severe anemia, and hypotension. Hypoglycemia is often also seen in cerebral malaria and severe malaria, especially in pregnant women. Other causes of CNS infection and encephalopathy must be excluded, and biochemical screening of blood and examination of cerebrospinal fluid (CSF) are mandatory.

Although cerebral malaria should be suspected in any person with impaired consciousness, fever, and recent travel to or residence in a *P. falciparum*-endemic country, confirming the diagnosis can be difficult. While demonstration of *P. falciparum* parasites in thick and thin blood smears should establish the diagnosis, one must consider the possibility of another cause for the impaired consciousness with coincident parasitemia. This concern is especially high for children from countries with high levels of asymptomatic parasitemia. In addition, the sensitivity and specificity of microscopy are operator dependent and can be problematic in nonendemic countries where laboratory technicians are not experienced in microscopic evaluation, or in resource-limited settings where diagnostic equipment is substandard or unavailable.

Several point-of-care diagnostics (now called rapid diagnostic tests or RDTs) based on immunoassays that detect specific parasite proteins have been developed and field-tested. These tests use a small amount of patient blood to determine if the patient is infected with a malaria species and if that species is *P. falciparum*; they are rapid and inexpensive. However, these tests are considered complementary to microscopy as they have poor sensitivity in patients with low parasite burdens; cannot determine the level of parasitemia; and do not differentiate between the non-*falciparum* species of malaria. Like microscopy, RDTs do not distinguish between cerebral malaria and coincidental parasitemia.

When cerebral malaria is a consideration, lumbar puncture should be performed to exclude other causes of encephalopathy. In cerebral malaria, CSF examination occasionally reveals elevated protein concentration or mild pleocytosis, especially if seizures have occurred. Hypoglycorrhachia is not a feature and indicates other causes.

A variety of abnormalities in laboratory tests may be observed in cases of *P. falciparum* malaria, including a normocytic, normochromic hemolytic anemia, leukopenia, monocytosis, thrombocytopenia, proteinuria, azotemia, elevated liver enzymes, and disseminated intravascular coagulation. With severe *P. falciparum* malaria, lactic acidosis, elevated blood creatinine, and hypoglycemia may be observed. Hypoglycemia, which is often seen in children and pregnant women or as a result of intravenous quinine therapy, may be responsible for deteriorating neurologic status and so must be recognized and treated.

Currently there is no diagnostic role for brain imaging in cerebral malaria, but there are studies using imaging to try to discern abnormalities specific to cerebral malaria, including prognostic factors and even pathophysiology. Fundoscopy should be performed since the presence of malaria retinopathy is the only reliable clinical feature that distinguishes cerebral malaria from other CNS pathologies.[2]

Severe malaria, including cerebral malaria, should be treated parenterally. The standard of care is now intravenous artesunate. To obtain artesunate in the United States, the CDC Malaria Hotline should be called (770-488-7788 anytime or 855-856-4713 Monday through Friday 9 A.M. to 5 P.M. EST). The dose of intravenous artesunate is weight based. For adults/children greater than 20 kg the dose is 2.4 mg/kg, while for children less than 20 kg the dose is 3.0 mg/kg. Appropriate doses are given at 0, 12, 24, and 48 hours. While awaiting the delivery of intravenous artesunate the CDC lists a number of enteral alternatives that can be given.[3] After the course of artesunate is administered, an oral course of antimalaria drugs should be given.[3] If oral medications cannot be given, then 7 days of intravenous artesunate, doxycycline, or clindamycin can be given.

After initiation of antimalarial therapy, patients with *P. falciparum* infection must be closely monitored for complications and response to treatment. Seizures should be treated with anticonvulsants, and frequent glucose monitoring is essential to manage hypoglycemia. Maintaining adequate fluid balance is critical in preventing further morbidity, especially in those with renal failure or pulmonary edema. Blood transfusions can be used to correct anemia, but can lead to significant fluid overload. The CDC no longer recommends exchange transfusions.

In an attempt to decrease the mortality and morbidity associated with severe malaria and cerebral malaria, many adjuvant therapies have been tried. Measures that have failed to show clinical improvement or made outcomes worse include broad immunosuppression (e.g., corticosteroids, intravenous immunoglobulins, cyclosporine), anti-TNF treatment (e.g., antitumor necrosis factor alpha antibodies or pentoxifylline), and prophylactic phenobarbital, mannitol, and antithrombotics (e.g., aspirin, ibuprofen, *N*-acetylcysteine, heparin). Other adjunctive therapies for severe malaria, not specifically cerebral malaria, are currently in trials or their outcomes have not yet been reported.

Cerebral Toxoplasmosis

Toxoplasma gondii is an obligate intracellular protozoan that naturally infects most warm-blooded animals from birds to humans. The prevalence of *T. gondii* infection in humans worldwide is estimated to be 25 to 30 percent but varies greatly by geographic location and socioeconomic status. Felids (i.e., cats) are the definitive hosts in which the sexual life cycle occurs, while the asexual life cycle occurs in intermediate hosts such as humans. Humans commonly become infected with *T. gondii* via ingestion of food or water contaminated with the persistent forms of *T. gondii* (i.e., bradyzoite-containing tissue cysts from intermediate hosts or sporozoite-containing oocysts excreted in the feces from acutely infected felids). As implied by being the "T" in the TORCH acronym for congenital infections, *T. gondii* can also be vertically transmitted in newly infected pregnant women, leading to the recommendation for pregnant women to avoid contact with cat feces. Infections have also been acquired through blood transfusions, organ transplantation, and accidental inoculation in laboratory workers, though these routes are quite rare.

Upon entry into humans, the sporozoite or bradyzoite, depending on the infective stage ingested, transforms into a tachyzoite that invades host cells and disseminates via the lymph and blood. The tachyzoite invades host cells and forms a protective parasitophorous vacuole within the cytoplasm. Like most intracellular microbes, the parasite modifies the host cell via the secretion of a number of effector proteins. How *T. gondii* crosses the blood—brain barrier to enter into the brain and retina has not been definitively determined, but evidence exists that *T. gondii*: (1) passes from the vasculature between endothelial cells; (2) infects endothelial cells and then ruptures across the basolateral side of the cell; or (3) is carried into the brain by infecting an immune cell that then travels across the blood—brain barrier. Tachyzoites infection is controlled by an intact T-cell response (CD8 cells more than CD4 cells) which produce interferon-γ. In skeletal and cardiac muscle and in the brain and retina, parasites switch to the bradyzoite form and establish cysts, which appear to provoke less of an immune response (Fig. 46-2). These cysts persist as reservoirs for reactivation or transmission.

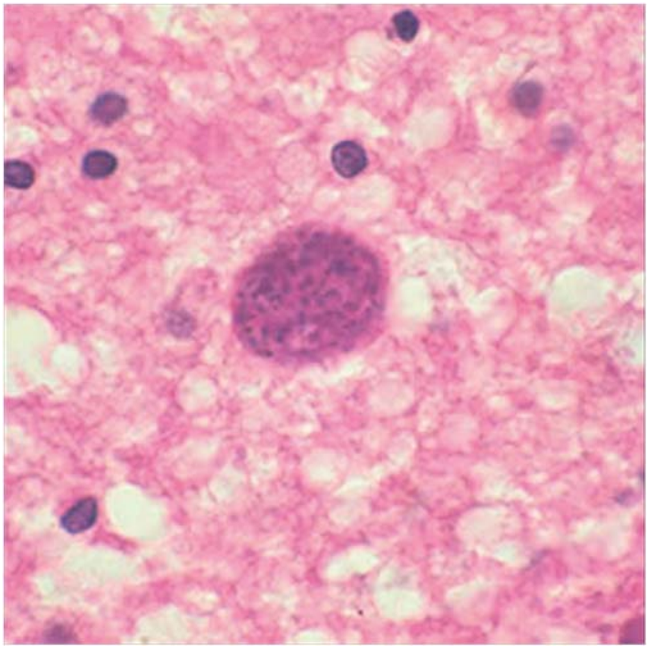

FIGURE 46-2 ■ *Toxoplasma gondii* cyst in brain tissue stained with hematoxylin and eosin. (From the US Centers for Disease Control and Prevention.)

Approximately 80 percent of primary toxoplasmosis infection is asymptomatic in immunocompetent adults. Nontender cervical adenopathy is most frequently seen among symptomatic individuals, but generalized adenopathy and a mononucleosis-like illness may occur. In the immunocompetent patient, the course of toxoplasmosis is usually benign and self-limited. A minority of patients can develop persistent lymphadenopathy or ocular toxoplasmosis. Ocular toxoplasmosis was previously thought to arise primarily from congenital infection, but more recent work suggests that it arises equally often from postnatally acquired *T. gondii* infection. Ocular lesions usually present as a focal, necrotizing retinitis with intense vitreal inflammation, showing a characteristic "headlight in fog" appearance. Relapses of chorioretinitis are frequent and are evident in the areas around the chorioretinal scars (Fig. 46-3).[4]

Congenital infection arises most commonly as a result of primary infection of the mother during gestation or 3 months prior to conception. Congenital infection can also occur in a chronically infected mother who is severely immunocompromised (e.g., AIDS) during gestation, or in a chronically infected pregnant woman

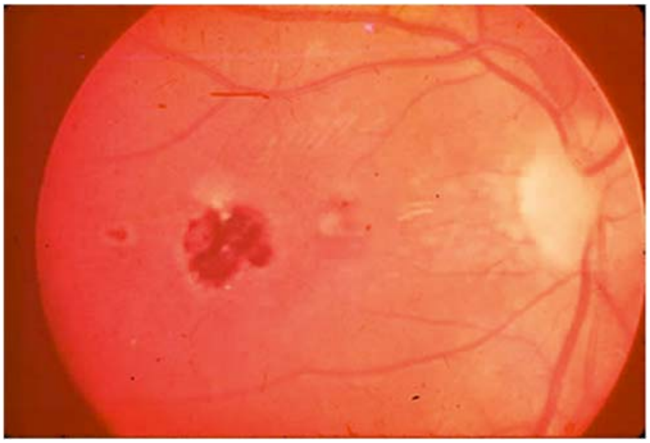

FIGURE 46-3 ■ *Toxoplasma* chorioretinitis: a pale, atrophied lesion containing black pigment. (From the US Centers for Disease Control and Prevention.)

who becomes infected with a new, highly virulent strain to which her prior infection does not confer immunity. Infection acquired in the first trimester is severe and can be associated with spontaneous abortion. Infection later in pregnancy shows more variable severity depending on individual factors. In the newborn, the presence of hydrocephalus, retinochoroiditis, or intracranial calcifications is suggestive of congenital toxoplasmosis and should be evaluated accordingly. Most infants are asymptomatic at birth but may present with overt symptoms, including severe developmental delay later in life.

Toxoplasmic encephalitis most commonly occurs as a result of reactivation of a latent infection which occurs in the setting of significant compromise of T-cell function (e.g., AIDS, organ transplant, and hematologic malignancies). In addition, immunosuppressants including steroids, mycophenolate mofetil, and adalimumab have been linked to rare cases of toxoplasmic encephalitis. In the immunocompromised, primary infection with *T. gondii* usually results in systemic or lung symptoms, rather than CNS involvement. Immunodeficient individuals with toxoplasmic encephalitis usually manifest with encephalitis, meningoencephalitis, or mass lesions (Fig. 46-4); therefore, toxoplasmic encephalitis often presents as a nonspecific decrease in mentation, seizures, or with focal neurologic findings. Frank meningismus is rare.

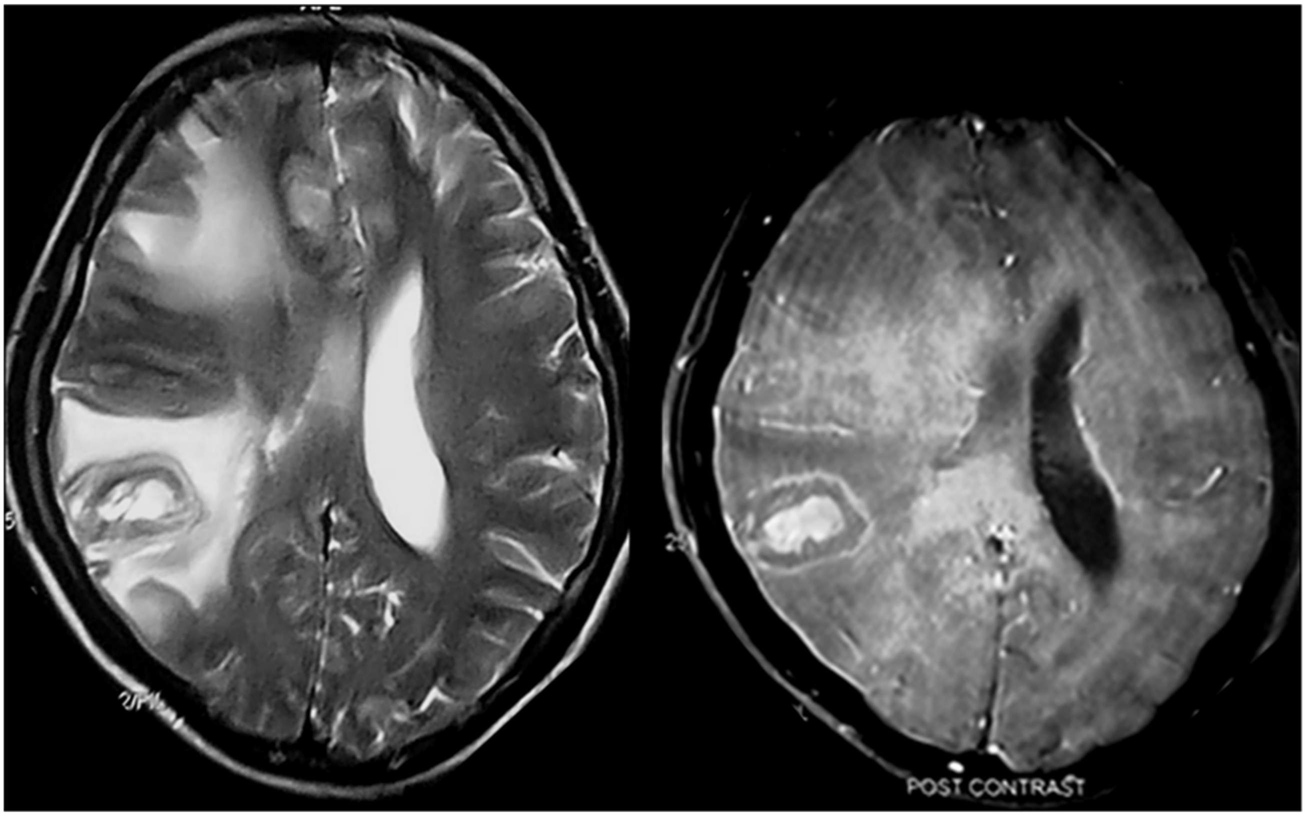

FIGURE 46-4 ■ Magnetic resonance imaging (MRI) of toxoplasmosis in a patient with AIDS. T2-weighted MRI showing the lesion with extensive perilesional edema (left); T1 contrast-enhancement of toxoplasmosis lesion (right). (Courtesy of Dr. Nicolette Mariano.)

The diagnosis of primary toxoplasmosis in immunocompetent hosts, transplant patients, and pregnant women is typically established through serology, either with a positive IgM to IgG seroconversion in paired sera or a twofold increase in IgG titers. Prenatal diagnosis can be confirmed by amniotic fluid polymerase chain reaction (PCR) or fetal ultrasound consistent with findings of congenital toxoplasmosis.[5] Most disease in immunocompromised hosts is reactivation disease, and the presence of IgG antibodies is suggestive of the diagnosis. Among HIV patients, toxoplasmic encephalitis usually occurs after the CD4 count has fallen to less than $100/\text{mm}^3$, although those with CD4 counts less than $200/\text{mm}^3$ are at risk for toxoplasmic encephalitis. If the patient is taking appropriate trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis, then even in the setting of a low CD4 count, toxoplasmic encephalitis is unlikely. Histology of brain biopsy specimens confirms the diagnosis but is impractical in most cases. PCR of serum, CSF, and biopsy tissue has been performed with varying degrees of success. CSF PCR is very specific, but the sensitivity is low (50%). For retinochoroiditis, the diagnosis is usually made by fundoscopic exam. Serology of aqueous humor in parallel with serum or PCR of the aqueous and vitreous can be used in cases where the clinical diagnosis is ambiguous.[4]

Cranial imaging should be performed in patients with suspected CNS toxoplasmosis. Neuroimaging usually reveals multiple ring-enhancing or solid lesions typically located in the gray matter; in HIV patients the cerebral cortex is more common than the basal ganglia, and thalamic locations are more likely than cerebellar (Fig. 46-4). In those with severe immunosuppression, atypical presentations with a lack of enhancement may occur. In infants, computed tomography (CT) is the method of choice, although ultrasound can be used. CSF findings are nonspecific and include mononuclear pleocytosis, elevated protein, and normal glucose. It should be noted that in the setting of mass lesions in the brain parenchyma, lumbar puncture is generally not recommended or indicated.

Definitive diagnosis of toxoplasmosis is made in the presence of a compatible clinical syndrome, consistent findings on magnetic resonance imaging (MRI), CT, or other imaging modalities, and detection of the protozoan in a clinical sample. AIDS patients with multiple enhancing cerebral lesions and with a positive IgG antibody should be presumed to have toxoplasmic encephalitis and started on empiric therapy and monitored for clinical and imaging improvement by 2 to 3 weeks following initiation of therapy. Biopsy is reserved for refractory cases, non-AIDS immunocompromised patients, or in AIDS patients with single lesions or those who are IgG negative.

Suspected or confirmed cases of ocular toxoplasmosis that is active and threatens vision should be treated. Several regimens have been used to treat it successfully, with a combination of pyrimethamine, sulfadiazine, and leucovorin being the most common regimen. Other regimens, including intravitreal clindamycin, are reviewed elsewhere.[4] The use of systemic steroids in combination with antiparasitic drugs is indicated for those with severe vitreous inflammation, affected vision, lesions close to the optic nerve or fovea, and large active lesions.[4]

Management of infected pregnant women varies considerably. Confirming a diagnosis of acute infection is essential due to the potential toxicity of the drugs used for treatment and for guiding decisions about termination of the pregnancy. Treatment indications and regimens for pregnant women and children with congenital toxoplasmosis are reviewed elsewhere.[5]

AIDS patients with CD4 counts less than 100 cells/mm^3 who develop reactivation toxoplasmic encephalitis should always be treated with at least two agents. The first-line treatment for toxoplasmic encephalitis is usually a combination of pyrimethamine and a sulfonamide. These antifolates are active against tachyzoites and are synergistic in combination. Pyrimethamine is lipid-soluble and readily penetrates the brain parenchyma even in the absence of inflammation. The usual regimen for adults is an oral loading dose of 200 mg of pyrimethamine followed by 50 to 75 mg daily for 3 to 6 weeks as well as sulfadiazine at a dose to 1 to 1.5 g orally every 6 hours for 3 to 6 weeks. The lower doses are for patients weighing less than 60 kg and the higher dose for those who weigh 60 kg or above. While patients are taking pyrimethamine and for 1 week after, patients should also receive folinic acid 10 to 20 mg orally daily; folinic acid alleviates some of the hematologic side effects associated with pyrimethamine. For those who are sulfa allergic, clindamycin orally or parenterally 600 mg every 6 hours or atovaquone 1,500 mg orally twice a day can be used in combination with pyrimethamine and folinic acid. In areas where pyrimethamine is not readily available, TMP-SMX (15 to 20 mg/kg daily of the trimethoprim component in three divided doses) has been found to be noninferior to pyrimethamine-based regimens.

For other alternative acute treatment options as well as for chronic treatment options for HIV/AIDS patients, please see the NIH guidelines.[6] Most non-HIV/AIDS immunocompromised patients will be treated with the same acute treatment regimens as listed above, but the chronic phase may differ and should be managed in conjunction with advice from other relevant medical specialists.

African Trypanosomiasis

Trypanosoma brucei is the causative agent of human African trypanosomiasis, which is also known as "sleeping sickness." Two distinct forms exist: western (chronic) sleeping sickness, due to infection by *T. brucei gambiense*, and eastern and southern (acute) sleeping sickness, caused by *T. brucei rhodesiense*. The tsetse fly, or *Glossina*, is the vector for *T. brucei*. Fewer than 1,000 new cases of human African trypanosomiasis were reported to the WHO in 2018, which represents a marked drop in cases over the last 20 years driven by sustained and focused efforts to treat patients with human African trypanosomiasis.

The majority of *T. b. gambiense* cases occur in the Democratic Republic of Congo, with the Central African Republic and Chad reporting far fewer cases. The disorder has a subacute course and is perpetuated mainly through chronically infected humans. East African trypanosomiasis (*T. b. rhodesiense*) occurs in the eastern and southern parts of equatorial Africa, especially Malawi and Uganda, and is typically acquired from zoonotic sources. It has a more fulminant course, with death occurring within a few weeks after infection, thereby decreasing the possibility of human reservoirs for infection. Most cases in travelers have been due to *T. b. rhodesiense*.

T. brucei undergoes several developmental stages in the tsetse fly over a life cycle of about 3 weeks. Upon ingestion with a blood meal, blood stream trypomastigotes become procyclic trypomastigotes in the insect midgut and divide rapidly. These then leave the midgut and transform into epimastigotes, eventually making their way into the fly's salivary glands. They change into metacyclic trypomastigotes, which are injected into the human or mammalian host with the blood meal. The metacyclic trypanosomes transform into the bloodstream form and invade extracellular spaces, including the blood, lymphatics, tissue fluids, and, eventually, the CNS via the CSF (Fig. 46-5).

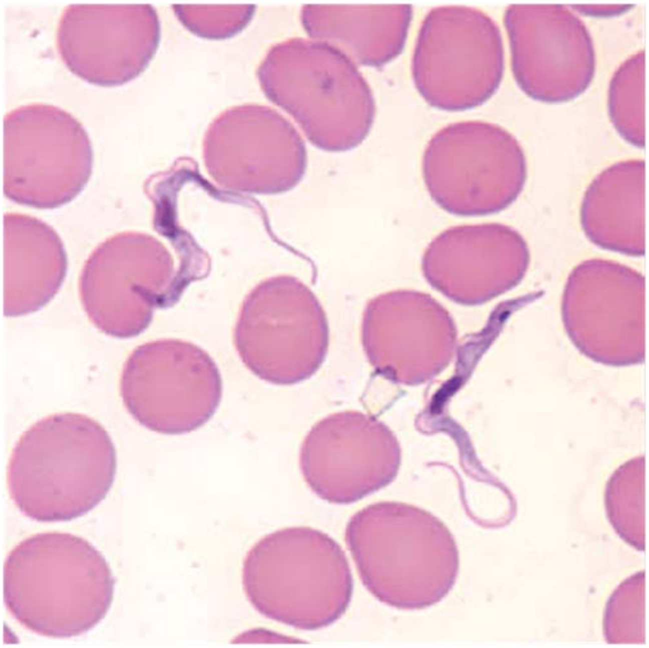

FIGURE 46-5 ■ African trypanosomes in thin blood smear. (From the US Centers for Disease Control and Prevention.)

Blood stream trypomastigotes evade the immune system by antigenic variation of their variant surface glycoproteins. In addition, *T. b. gambiense* and *T. b. rhodesiense* are resistant to killing by human apolipoprotein A1, which is a major trypanolytic factor that protects humans against other *T. brucei* subspecies infection. *T. b. gambiense* and *T. b. rhodesiense*'s resistance to this protein underlies their ability to cause systemic human infections.[7]

Clinically *T. brucei* disease is divided into two stages: the hematolymphatic stage (stage 1) and the meningoencephalitic stage (stage 2), with *T. b. gambiense* having a more prolonged course (mean time to death 3 years) and *T. b. rhodesiense* being relatively rapid (death within 6 months). While progressive untreated disease generally results in death, asymptomatic carriers and spontaneous cures have been reported for *T. b. gambiense* infections. The earliest clinical manifestation is a local, hard, painful lesion (trypanosomal chancre) at the site of the insect bite, which is more common in *T. b. rhodesiense* infection and rare with *T. b. gambiense*. Histologic examination of the chancre shows a lymphocytic infiltrate with dividing trypanosomes. Shortly afterward, widespread dissemination of the organism occurs via the blood stream and lymphatics. Lymphadenopathy of the posterior cervical regions (i.e., Winterbottom sign) is typical in *T. b. gambiense* infection, while *T. b. rhodesiense* more commonly causes submandibular, axillary, and inguinal lymphadenopathy. The first stage of *T. b. gambiense* infection can result in days to months of intermittent fever, headache, hepatosplenomegaly, and endocrine dysfunction. For *T. b. rhodesiense*, the first-stage symptoms are similar but less prolonged. Of note, travelers to endemic areas are more likely to present with chancres for either *T. brucei* infection and the incubation period is often shorter (<3 to 4 weeks). With progression of the disease, the systemic episodes decline in severity. The second stage occurs as the trypanosomes cross the blood–brain barrier and enter the brain. In this stage, sleep and neuropsychiatric symptoms predominate. These symptoms include daytime sleepiness, night-time insomnia, and abnormalities on polysomnography. In addition, a range of behavioral changes can also occur, including personality changes (e.g., emotional lability, aggression, apathy, or mania), confusion, and frank dementia. As the disease progresses, the neurologic manifestations become more severe, culminating with coma and death.[7]

Definitive diagnosis relies on observation of trypanosomes in aspirates from lymph nodes or concentration techniques used on blood or CSF. For *T. b. rhodesiense*, since the parasitemia level is higher, if concentration techniques cannot be done, motile trypanosomes may be visualized on nonconcentrated thin or thick blood smears in the early stages. The card agglutination trypanosomiasis test, which detects specific antibodies, is of value for screening of at-risk patients for *T. b. gambiense* but usually requires parasitologic confirmation as all areas of the world now have very low prevalence rates (<0.1%). CSF examination is essential for stage determination but cannot be used for definitive diagnosis of *T. brucei* disease unless trypanosomes are seen on microscopic examination.

Drug treatment is dependent on the stage of illness and the type of trypanosomiasis. The first stage is defined as patients with the diagnosis of *T. brucei* infection with a CSF leukocyte count of $5/\text{mm}^3$ or less and no trypanosomes visualized on CSF (i.e., no obvious CNS involvement), and the second stage is defined as those with CSF leukocyte counts greater than $5/\text{mm}^3$ or trypanosome visualization. For *T. b. gambiense*, with the approval of fexinidazole, second-stage disease is now subdivided in nonsevere (CSF WBC less than $100/\text{mm}^3$) or severe (CSF WBCs greater than $100/\text{mm}^3$). In *T. b. gambiense* infection, for people age 6 or older and body weight greater than or equal to 20 kg, those with first stage or nonsevere second stage should be treated with fexinidazole, while those with severe second stage (regardless of age or weight) should be treated with a nifurtimox-eflornithine combination therapy. Further details about *T. b. gambiense* treatment, including alternative therapies, are defined elsewhere.[8] For *T. b. rhodesiense*, first-stage disease is treated with suramin and second-stage disease with melarsoprol.[7] Melarsoprol is reserved for *T. b. rhodesiense* second-stage disease because it has a high rate of serious adverse reactions, including an encephalopathy syndrome that has a high mortality rate.

Primary Amebic Meningoencephalitis and Granulomatous Amebic Encephalitis

Primary amebic meningoencephalitis is an acute, rapidly progressive, necrotizing meningoencephalitis caused by the free-living ameba *Naegleria fowleri*. Despite the widespread distribution of *N. fowleri*, the disease is relatively rare and is associated with exposure to warm fresh water. In the United States, over 80 percent of the cases have occurred in the summer months and primarily in the most southern states, although Kansas, Missouri, and Minnesota have recently reported cases.

Infection is acquired when water containing the ameba is accidentally inhaled. Thus, most cases of *N. fowleri* are associated with recreational activities in warm freshwater lakes, though cases of *N. fowleri* have occurred in children bathing or playing in untreated well water or underchlorinated municipal water, as well as in adults who used *N. fowleri*–contaminated water for nasal irrigation. The ameba rapidly invades the olfactory neuroepithelium, gaining access to the brain through the cribriform plate. *Naegleria* infection initially involves the superficial gray matter with eventual extension to the deep matter and cerebellum. Prominent involvement of the frontotemporal areas, olfactory bulbs, and subarachnoid space has been observed. Neutrophil invasion, extensive necrosis, and vascular invasion are typical. The pathogenesis of infection likely involves multiple mechanisms, including secretion of lytic enzymes, elucidation of apoptotic factors, production of membrane pore-forming proteins, and direct feeding by the amoeba, resulting in a marked cytopathic effect.

Patients usually present within 5 days from exposure, although incubation periods of up to 14 days have been reported. The symptoms are commonly consistent with acute bacterial meningitis, including severe headache, fever, lethargy, nausea, and vomiting. Olfactory involvement, manifesting as nasal stuffiness or changes in smell, may be a clue to the etiology. Seizures, nuchal rigidity, and confusion, followed by coma, usually develop within days. Focal neurologic signs are rare. The patient then rapidly deteriorates and death occurs within a week. Brainstem herniation due to inflammation and increased intracranial pressure is the usual cause of death.

CSF findings are typical of acute bacterial meningitis with an elevated opening pressure, neutrophilic pleocytosis, low to normal glucose, and elevated protein levels. Elevated CSF red blood cells occur late in the course. If *N. fowleri* is suspected, a wet mount of CSF should be performed as it may show mobile trophozoites. Ideally the wet mount should be done rapidly after CSF collection as ameba may adhere to the container. Giemsa or Wright stain can help differentiate the trophozoite from host cells (Fig. 46-6). *N. fowleri* can also be identified through PCR of CSF or brain tissue or via commercially available next-generation sequencing of DNA or RNA obtained from CSF or brain tissue. Ameba can also be detected by immunohistochemical means on formalin-fixed brain.

Only a few survivors of primary amebic meningoencephalitis have been reported, likely because of delays in diagnosis, the rapid progression of symptomatic disease, and the lack of clarity regarding best treatments. Most survivors have received high-dose intravenous amphotericin as well a combination of additional drugs such as fluconazole, azithromycin, rifampin, and miltefosine. In addition, treatment should address elevated intracranial pressure and brain edema with the use of adjunct therapies such as dexamethasone, CSF drainage, hyperosmolar therapy, and even induced hypothermia. The Centers for Disease Control and Prevention Emergency Operation Center (open 24/7, 770-488-7100) can help with diagnostic and treatment recommendations. Of note, a recent case of supposed primary amebic meningoencephalitis, originally diagnosed as viral meningitis, with spontaneous recovery of the patient, was determined to be caused by a *Paravahlkampfia* species. This case raises the possibility that the rare survivors of primary amebic meningoencephalitis, in times prior to definitive molecular diagnostics, were infected with other free-living ameba rather than *N. fowleri*.[9]

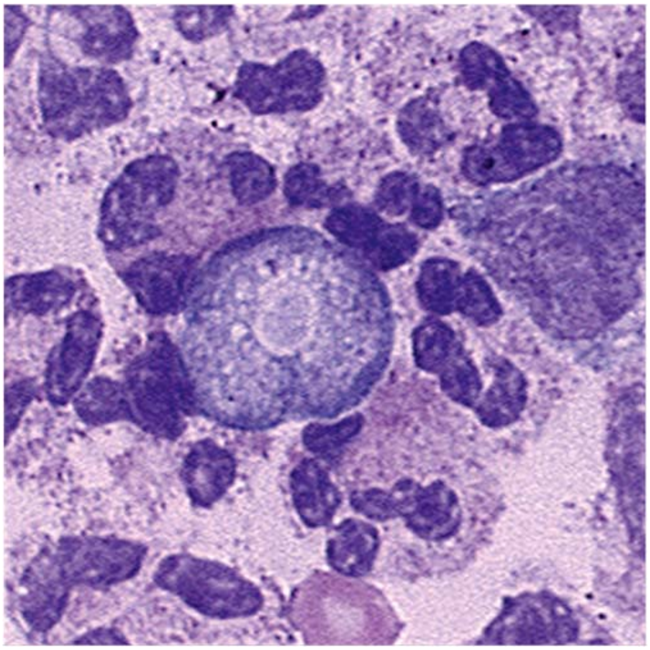

FIGURE 46-6 ▪ Primary amebic meningoencephalitis. *Naegleria* trophozoite in CSF. (From the US Centers for Disease Control and Prevention.)

Granulomatous amebic encephalitis is a subacute, indolent, usually fatal meningoencephalitis caused by either of two species of free-living ameba, *Acanthamoeba* spp. or *Balamuthia mandrillaris*.

Acanthamoeba spp. have been isolated across the globe from air, water, and soil. *Balamuthia* also is ubiquitous, though it is more commonly isolated from soil than water. Like *N. fowleri*, based on serology positivity, many people are presumed to be exposed to *Acanthamoeba* spp. and *Balamuthia* with the development of clinical disease being relatively rare. Humans are thought to become actively infected with either agents of granulomatous amebic encephalitis via the lower respiratory tract or broken skin. While *Acanthamoeba* disease primarily occurs in immunocompromised people, *Balamuthia* disease occurs more often in the immunocompetent, though it can also occur in the immunocompromised. In the United States, *Balamuthia* infection is seen more often in males, those of Hispanic race, and residents of the southern latitudes of the United States. The increased risk of *Balamuthia* infection in males and Hispanics may be due to an increased risk of exposure (i.e., more likely to be exposed to soil) or yet-to-be-defined genetic risk factors. Several cases of *Balamuthia* have occurred via transplantation of organs from persons not recognized to be infected with *Balamuthia*.

Acanthamoeba granulomatous amebic encephalitis has an insidious onset of symptoms, and presents with both nonspecific complaints, such as mental status changes and fever, as well as focal abnormalities including seizures, hemiparesis, and ataxia. As the disease progresses, increased intracranial pressure eventually causes lethargy and coma, with death occurring due to brain herniation. *Balamuthia* disease can present either with subacute or chronic symptoms as described earlier and can result in death within a week or over months after the onset of symptoms.

Space-occupying or ring-enhancing lesions, either single or multiple, on neuroimaging are characteristic of granulomatous amebic encephalitis. Rarely, *Balamuthia* infection can also demonstrate hemorrhage within the ring-enhancing lesions. CSF, when obtained, typically shows a lymphocytic pleocytosis, increased protein concentration, and slightly low or normal glucose level. Unlike primary amebic meningoencephalitis, identifying ameba in the wet mount is uncommon but has been reported. Serologic tests for either *Acanthamoeba* or *Balamuthia* are not helpful. Tissue diagnoses are most common, and unfortunately often occur at autopsy. To definitively distinguish the causative agent of granulomatous amebic encephalitis, either ameba-specific immunohistochemistry on tissue sections or molecular diagnostics (e.g., PCR, next-generation sequencing) on RNA or DNA isolated from tissue or CSF must be done. Of note, *Acanthamoeba* spp. and *Balamuthia* can both present with preceding skin lesions, which should be biopsied if present.

Akin to primary amebic meningoencephalitis, the limited number of patients diagnosed premortem and of survivors means no definitive treatment regimens have been defined. In general, treatment of granulomatous amebic encephalitis usually involves multidrug regimens that include some combination of pentamidine, an azole (e.g., fluconazole for *Balamuthia*), sulfadiazine, flucytosine, miltefosine, and amikacin (for *Acanthamoeba*) or azithromycin/clarithromycin (for *Balamuthia*). Even in the setting of early recognition and aggressive therapy, most patients with granulomatous amebic encephalitis will die.

Cerebral Amebiasis due to *Entamoeba histolytica*

Amebiasis is disease caused by *Entamoeba* spp., some of which are nonpathogenic and some of which cause diarrhea only. *Entamoeba histolytica* causes tissue-invasive disease, including cerebral abscesses. Amebiasis most commonly occurs in socioeconomically deprived communities in developing countries, travelers returning from these areas, chronically institutionalized individuals, and men who have sex with men.

Infection occurs by ingestion of cysts with sources including fecal–oral transmission and contaminated food or water. Excystation occurs in the small intestine, producing trophozoites. The parasite colonizes the colon where some trophozoites encyst and are passed in the stool to begin the cycle anew. Invasive disease begins when trophozoites invade the colonic mucosa leading to inflammatory colitis. Extraintestinal spread is rare and most frequently involves the liver, which can then lead to spread locally or distally (lungs, genitourinary system, skin, and brain). Approximately 80 percent of the patients with a liver abscess are young–middle aged men.

Cerebral abscesses occur in 1 to 5 percent of those with liver abscesses and present with the findings of a space-occupying lesion such as focal findings, seizures, mental status changes, and headache. CSF findings are nonspecific, including a pleocytosis and an elevated protein; lumbar puncture is not necessarily recommended. CT and MRI findings will be consistent with an abscess.

Cerebral amebiasis is often diagnosed clinically (e.g., cerebral abscess in a patient with an amebic liver abscess or recently treated liver abscess) as there is no specific, proven diagnostic test. In liver abscesses, PCR of the abscess fluid or antigen detection from the serum or abscess fluid can be performed. In addition, serologic testing can be a useful adjunct with the recognition that serologies can be negative early in disease and that a positive serology in a patient coming from an endemic region does not distinguish prior disease from current disease or unrelated coinfection. Stool microcopy is very low yield in these patients and is not recommended.

Like bacterial brain abscesses, the treatment is generally a combination of surgical drainage and antimicrobial therapy (metronidazole) for 6 or more weeks.[10]

HELMINTHIC INFECTION

Due to their relatively large size (50 μm up to 15 m), these parasites pose a distinct problem for host immunity. Helminths capable of causing CNS disease are diverse, with complex life cycles involving both human and nonhuman animal hosts during different stages of their development. Helminths are generally identified by taxonomic class [i.e., as cestodes (tapeworms), nematodes (roundworms), or trematodes (flukes)]. Except for disease caused by *Taenia solium* (tapeworm), helminth infections of the CNS are rare to extremely rare. Thus, this section will focus on *T. solium* with very brief comments about other helminths. Table 46-1 includes a summary of the most common helminths that cause CNS infections.

Cestodes

CYSTICERCOSIS

Humans are the definitive host for the tapeworm *T. solium*, meaning that adult tapeworms develop in the human intestine. The adult worm sheds proglottids, or eggs, which contaminate the environment. Pigs develop *T. solium* tissue cysts after ingesting food or water contaminated with *T. solium* eggs. Adult tapeworms then develop in humans who eat undercooked tissue cyst-containing pork, completing this part of the *T. solium* life-cycle. Like pigs, humans can act as intermediate hosts and develop invasive disease (cysticercosis) if they ingest eggs. Current epidemiology suggests that humans develop cysticercosis or neurocysticercosis from human-to-human transmission, rather than from the environment. *T. solium* is endemic in most of Central and South America, China, India, southeast Asia, and sub-Saharan Africa. Imported cases of *T. solium* disease are seen in many developed countries.

After the eggs are ingested, oncospheres are liberated, penetrate the bowel wall, and enter the blood stream. These disseminate widely, favoring muscle and subcutaneous tissue. Larval forms develop and mature into cysticerci. Neurocysticercosis occurs when cysticerci develop in the eye, brain, or spinal cord.

A cysticercus is made up of an invaginated scolex surrounded by a vesicular wall. In the brain parenchyma, vesicular cysticerci elicit little or no inflammatory reaction. As the cysticercus involutes, it passes into the colloidal stage characterized by a mononuclear infiltrate surrounding the cysticercus with surrounding edema and gliosis due to the release of parasite antigens. Neurologic symptoms begin to manifest at this point. As further involution occurs (granular and calcific stages), edema decreases but astrocytic changes lead to the formation of granulomas with multinucleated giant cells. Persistence of these abnormal areas of tissue results in foci that can lead to recurrent seizures. Ultimately, the lesion will be cleared, leaving parenchymal calcifications. The role of calcified parenchymal lesions in recurrent seizures is controversial.

While most cases of neurocysticercosis are parenchymal and present with seizures, extraparenchymal disease does occur and can lead to more severe manifestations including death. Extraparenchymal cysticerci may develop in the subarachnoid, ventricular, or basal cisterns, and can cause hydrocephalus, arachnoiditis, and meningeal inflammation. Subarachnoid cysts may grow abnormally, causing grape-like cystic masses referred to as racemose cysticercosis.

Seizures—focal or generalized—are the primary or sole manifestation in 70 percent of cases, though focal neurologic deficits, including stroke-like syndromes and cognitive decline, can also occur. The severity and type of manifestations are dependent on lesion location (e.g., parenchymal vs. subarachnoid), the quantity of the lesions, and the host immune response. Spinal cord cysticercosis may lead to compressive myelopathy or radiculopathy. Ocular disease can cause visual field defects, decreased acuity, and blindness from vitritis, uveitis, or endophthalmitis.

Neurocysticercosis is usually diagnosed by exposure history supported by compatible symptoms, serology, and neuroimaging. Travel to endemic areas or previous residence in an area of high prevalence should alert clinicians to the possibility of the disease. Clinical symptoms are nonspecific, and routine laboratory testing does not show any typical abnormalities (e.g., cysticercosis is not associated with eosinophilia). Diagnostic criteria that stratify patients into definitive or probable diagnoses of neurocysticercosis have been developed and are based on neuroimaging, fundoscopic findings, serology, and epidemiology.[11]

Neuroimaging is an important component of the diagnosis of neurocysticercosis. Most patients have fewer than 10 cysts, which may be up to 5 cm in diameter, and many will have a single lesion. Patients from endemic countries may show *T. solium*-related calcifications, which are usually less than 1 cm in diameter, round, and are rarely found in the brainstem or cerebellum. Extraparenchymal disease can cause hydrocephalus. Arachnoiditis can manifest as leptomeningeal enhancement.

The identification of a cyst with a scolex (head of the tapeworm) on MRI or CT definitively makes the diagnosis of neurocysticercosis (Fig. 46-7). Nondiagnostic imaging findings—cystic lesions without a scolex, multilobulated subarachnoid lesions, resolution of cystic lesions after antiparasitic treatment or spontaneously if a single enhancing cystic lesion—are considered consistent with a diagnosis of neurocysticercosis but require meeting other criteria (e.g., serology or known household member with *T. solium* infection) to make a definitive diagnosis.[11]

T. solium antibody detection performed with enzyme-linked immunoelectrotransfer blot (EITB) is the test of choice and more sensitive from serum than CSF and in patients with subarachnoid disease or more than one viable cyst. In a patient with a single lesion, the EITB sensitivity drops to less than 60 percent. If EITB testing is not available, and if the patient has multiple viable CNS lesions, detection of anti-*T. solium* antibodies in the CSF by ELISA shows high sensitivity (89%) and specificity (93%). Detection of *T. solium* antigen in CSF or serum remains controversial. CSF findings are otherwise nonspecific and include a monocytic pleocytosis, mild elevations in protein; sometimes the presence of eosinophils in the CSF is a clue to diagnosis.

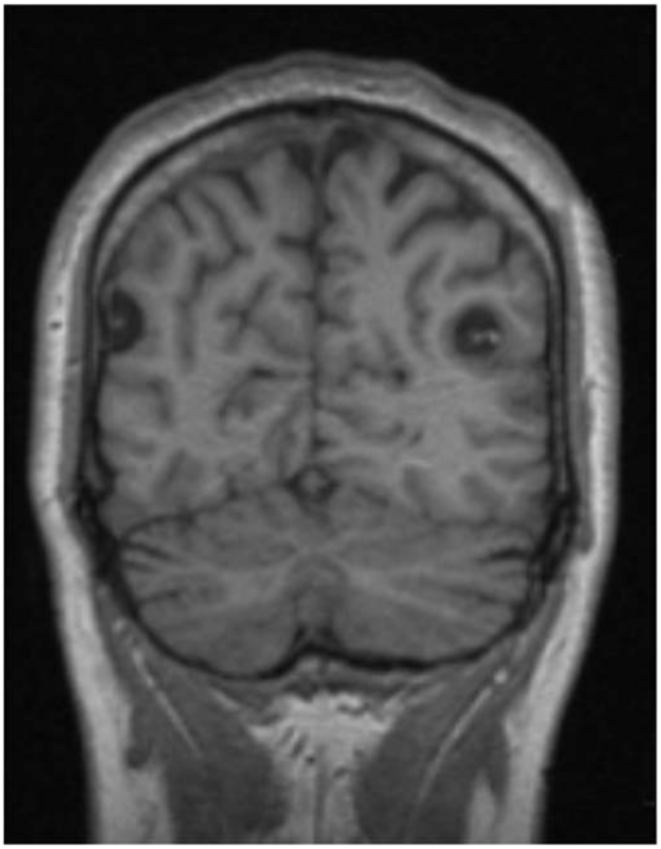

FIGURE 46-7 ▪ Coronal T1-weighted MRI showing neurocysticercosis.

Treatment guidelines have recently been updated for neurocysticercosis.[12] Prior to treating parenchymal disease with antiparasitic medications, fundoscopic examination should be done to rule out an ocular neurocysticercosis lesion. Treatment in patients with unrecognized ocular disease has the potential to provoke a strong hyperinflammatory ocular response that could lead to vision loss. Albendazole 15 mg/kg per day divided into two doses and corticosteroid treatment for 10 to 14 days are recommended for patients with one to two parenchymal viable or degenerating cysts. For more than two viable or degenerating cysts, combination therapy with albendazole (15 mg/kg per day), praziquantel (50 mg/kg per day), and corticosteroids for 10 to 14 days is recommended. For those with *T. solium* encephalitis (diffuse cerebral edema), corticosteroids alone are recommended. No antiparasitic or immunosuppressive therapy is recommended for those who only have neurocysticercosis-associated calcifications. Surgical removal of the cyst with no antiparasitic therapy is recommended for ocular disease. Intraventricular disease, subarachnoid disease, and spinal disease are considerably more complicated in terms of therapy and will require coordinated efforts from neurosurgeons, neurologists, and infectious disease specialists.[12]

First-line, single-drug anticonvulsant medication is usually adequate to control seizures. Optimal length of treatment is unclear, and withdrawal is typically followed by recurrence in about half of patients, despite an adequate antihelminthic course. Calcified parenchymal lesions may indicate the need for long-term antiseizure medication.

ECHINOCOCCOSIS (HYDATID DISEASE) AND SPARGANOSIS

Rarely, other cestodes may cause human CNS disease. Infection with *Echinococcus* spp. (most commonly *Echinococcus granulosus* and *Echinococcus multilocularis*), which are canine tapeworms, is called echinococcosis. Sparganosis is caused by infection with the diphyllobothroid tapeworms of the *Spirometra* genus. Humans are intermediate hosts for these worms and become infected through eating contaminated food. CNS disease in echinococcosis or sparganosis is extremely rare but can present with a variety of manifestations (e.g., focal brain or spinal cord symptoms or meningitis) depending on the location of the lesion and state of the inflammatory response. CNS cysts from *E. granulosus* are usually associated with cysts elsewhere in the body (Fig. 46-8).

E. granulosus is found in all continents, with the highest prevalence occurring in northeast Africa,

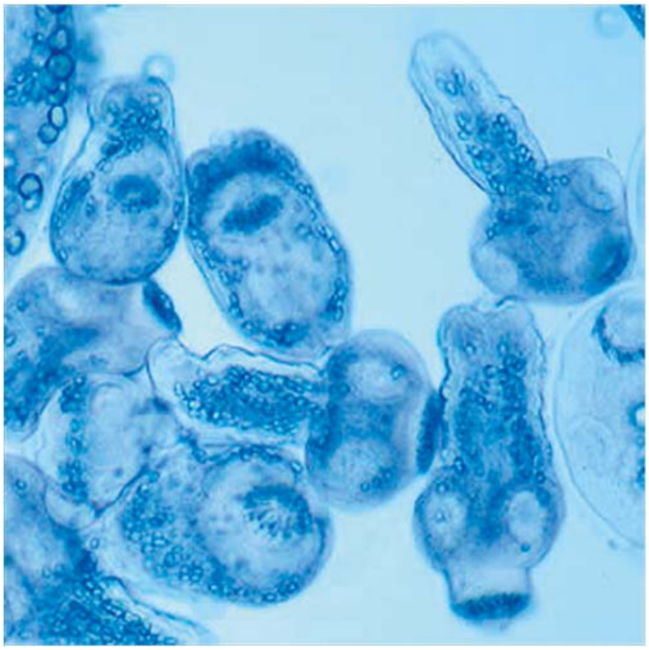

FIGURE 46-8 ▪ *Echinococcus* sp. protoscoleces. (From the US Centers for Disease Control and Prevention.)

South America, and Eurasia, while *E. multilocularis* is restricted to the northern hemisphere. Sparganosis is associated with eating undercooked frog or snake meat and primarily occurs in China and other parts of east and southeast Asia, though sporadic cases have been reported across the globe. Treatment for echinococcosis and sparganosis often requires both surgical interventions as well as antiparasitic therapy.

Nematodes

DISSEMINATED STRONGYLOIDIASIS

Strongyloides stercoralis is a gastrointestinal nematode endemic to humid tropical regions, including Southeast Asia, Africa, and Latin America, as well as the southeastern United States and southern Europe. Travel to or migration of patients from these areas accounts for most disease seen in temperate regions. Most infections are asymptomatic and may persist for decades due to the worm's ability to complete its full life cycle within humans. In the setting of human T-cell lymphotropic virus type 1 coinfection or immunosuppression—most commonly corticosteroids—*Strongyloides* can cause a hyperinfection syndrome in which autoinfection leads to increased numbers of worms in the gut (Fig. 46-9). This increase in gut worm burden can result in disseminated disease, which occurs when the larvae migrate away from the lungs and gastrointestinal tract into other organs. Large numbers of larvae migrating from the gut carry enteric bacteria into the bloodstream, which can cause acute bacterial meningitis and sepsis. The diagnosis of hyperinfection syndrome is usually made on finding larvae in stool in patients with a compatible systemic syndrome. Treatment includes aggressive antibiotic treatment for bacterial superinfection and ivermectin, the antihelminthic drug of choice.

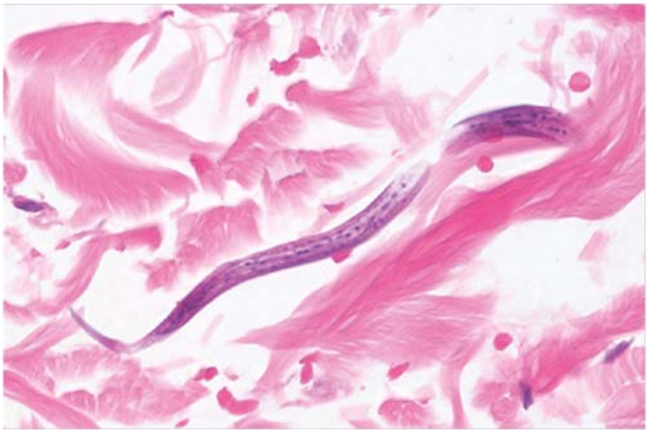

FIGURE 46-9 ■ *Strongyloides stercoralis* larva in tissue (intestine). (From the US Centers for Disease Control and Prevention.)

TRICHINOSIS

Trichinella spp. infection is acquired by ingestion of contaminated undercooked or raw pork (*Trichinella spiralis*) or game meat including walrus and bear meat. Infectious cysts in striated muscle tissue are digested, releasing larvae which mature into adults in the small intestine. The adult forms release newborn larvae in a few weeks. The newborn larvae disseminate in lymph and blood and cause symptoms of trichinosis by invading various body tissues. Modern farming practices have made cases of trichinosis increasingly rare, although outbreaks still occasionally occur.

Trichinosis has several phases. First, patients have gastrointestinal symptoms (from local infection) such as diarrhea, vomiting, and abdominal pain. Subsequently, with systemic dissemination, patients can experience fever, myalgias, malaise, headache, and periorbital and facial edema. The invasion of muscle can mimic an inflammatory myositis with an elevated creatinine kinase. Trichinosis is usually associated with peripheral eosinophilia. In patients with high parasite burdens, larvae can migrate into the CNS causing meningitis or encephalitis.

The diagnosis is made by positive serology (available through the CDC) in those who have a recent history of eating undercooked or raw pork or wild game meat. If necessary, a muscle biopsy demonstrating *Trichinella* larvae (Fig. 46-10) can be performed.

Treatment with albendazole or mebendazole, which kill the adult worms, is most effective during the gastrointestinal stage of disease. If the diagnosis is not made until the systemic phase of the disease, treatment may be less effective although it is still recommended. In the systemic phase of disease or in severe disease, adjunctive corticosteroids may be used.

ANGIOSTRONGYLUS CANTONENSIS

Angiostrongylus cantonensis is a rat worm in which snails and slugs are intermediate hosts. *A. cantonensis* is a common cause of eosinophilic meningitis in Southeast Asia and the Pacific Basin, which includes Hawaii. Humans become infected by eating infective larvae in raw or undercooked mollusks (intermediate hosts); other animals that eat the intermediate hosts (prawns,

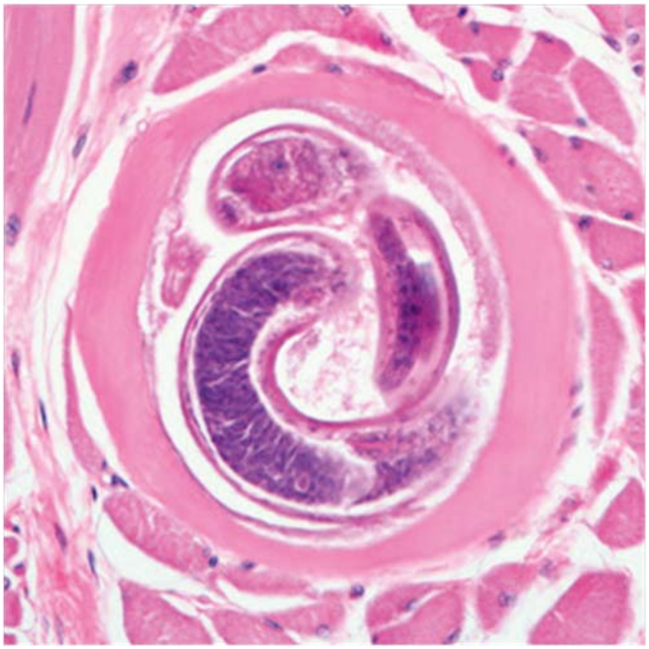

FIGURE 46-10 ■ *Trichinella spiralis:* encysted larva in muscle tissue. (From the US Centers for Disease Control and Prevention.)

crabs, frogs, lizards, flatworms); or contaminated vegetables. Patients commonly present 1 to 4 weeks after exposure and with signs and symptoms of acute meningitis. Patients often have sensory symptoms such as hyperesthesia or paresthesias and peripheral eosinophilia, though the lack of sensory symptoms or peripheral eosinophilia does not rule out *A. cantonensis* infection. Pleocytosis with or without eosinophilia, mild elevations in protein, and normal CSF glucose are commonly seen in *A. cantonensis* meningitis.

The diagnosis is primarily made clinically, although a recent outbreak and increased incidence in Hawaii led the Hawaii State Department of Health Laboratories to develop a PCR-based test for CSF.

Treatment is generally high-dose corticosteroids with emerging evidence for concurrent albendazole treatment. Given concerns regarding albendazole-related parasite death causing a hyperinflammatory response, albendazole treatment by itself is not recommended for neuroangiostrongyliasis. Most patients have a good recovery.[13]

GNATHOSTOMA *SPP.*

Gnathostoma spp. are nematodes with several definitive hosts (felids, canines, pigs, and boars) and a complex life cycle that involves two stages of intermediate hosts (copepods and then fish and frogs). *Gnathostoma* spp. are endemic in Southeast Asia, especially Thailand, with increasing infections in Mexico and Central and South America. Humans become infected by eating infective larvae in raw or undercooked intermediate hosts (primarily fish or frogs) or other animals that eat the intermediate hosts (birds, rats, snakes). Most commonly, *Gnathostoma* spp. cause early gastrointestinal symptoms followed by migratory subcutaneous swellings and peripheral eosinophilia about 3 to 4 weeks after exposure. *Gnathostoma* spp. migrate to the CNS less frequently than *A. cantonensis* but the disease caused by *Gnathostoma* is often more severe. Depending on where the larvae migrate, persons with gnathostomiasis can develop spinal cord or root syndromes and subarachnoid or intracranial hemorrhages.

Diagnosis of neurologic involvement of *Gnathostoma* spp. is usually made by the appropriate history (ingestion of raw food likely to be contaminated with infective larvae; migratory subcutaneous swelling) with a positive serology, though serologic testing is not available in the United States. CSF findings are akin to those seen with *A. cantonensis* except that frank blood or xanthochromia is more common in gnathostomiasis. Peripheral eosinophilia is also common. Neuroimaging studies can show hemorrhagic tracks consistent with worm migration.

Besides supportive care, there are no clear treatment guidelines for *Gnathostoma*-caused CNS disease. No evidence exists for the utility of corticosteroids, and antihelminth regimens (albendazole or ivermectin) may make the patient's neurologic status worse. Patients with mild or minimal neurologic symptoms/signs may recover, but those with severe symptoms have a poor prognosis.[13]

VISCERAL LARVAL MIGRANS: TOXOCARA *SPP. AND* BAYLISASCARIS PROCYONIS

Toxocara canis and *Toxocara catii* are dog and cat helminths, while *Baylisascaris* is a raccoon helminth. Humans, usually children, are infected by ingestion of eggs shed from the definitive hosts with *T. canis* being the most common cause of visceral larva migrans in the United States. *Toxocara* spp. commonly cause ocular toxocariasis and very rarely eosinophilic meningitis. Symptomatic *Baylisascaris* disease, which is extremely rare, can cause ocular infection as well as meningitis and spinal cord disease. Peripheral eosinophilia and

CSF eosinophilic pleocytosis can be seen with *Toxocara* or *Baylisascaris* CNS infection. *Toxocara* serologic testing is commercially available, while *Baylisascaris* serology from serum or CSF can be performed at the CDC. For ocular toxocariasis, corticosteroids are recommended, but their role in treatment of other CNS syndromes is unclear. For CNS disease with *Toxacara* spp. or *Baylisascaris*, the role of antihelminth drugs is unclear, but albendazole is the treatment of choice for either disease because it penetrates the CNS well and has low toxicity.

ONCHOCERCA VOLVULUS AND LOA LOA

Onchocerca volvulus and *Loa loa* are transmitted from human to human by biting flies *Simulium* and *Chrysops*, respectively. *O. volvulus* larvae can migrate to the eye where death of the larvae can cause ocular disease including blindness (commonly known as "river blindness"). *O. volvulus* primarily causes disease in sub-Saharan Africa, though Brazil, Venezuela, and Yemen are also sites of onchocerciasis. Loiasis is found in Central Africa, especially in the areas of Cameroon, Central African Republic, Democratic Republic of Congo, Equatorial Guinea, Gabon, and Sudan. Ivermectin treatment of onchocerciasis can precipitate severe adverse reactions (e.g., encephalitis, coma, and sometimes death) in patients with concomitant *L. loa* infections. Thus, in areas where both *O. volvulus* and *L. loa* are endemic, patients should be screened for *L. loa* microfilarie prior to commencing treatment with ivermectin for *O. volvulus*.

In addition to river blindness, limited evidence suggests that *O. volvulus* may play a role in nodding syndrome, which is a relatively uncommon pediatric disease primarily found in Uganda, Tanzania, and southern Sudan. It begins with "nodding episodes" which are frequent but brief bouts of loss of neck muscle tone associated with generalized seizure activity on electroencephalogram. Nodding syndrome can progress, with children showing cognitive decline, growth retardation, and psychiatric manifestations. Several studies have shown that patients with this syndrome are almost twice as likely to have skin snips with *O. volvulus* microfilarie compared to control patients, but no evidence for direct CNS infection by *O. volvulus* has been identified. Thus, how *O. volvulus* might cause nodding syndrome or even whether *O. volvulus* truly plays a role in its development remains unknown.[14]

Trematodes

SCHISTOSOMIASIS

Schistosoma spp. are trematode helminthic parasites acquired by contact with fresh water harboring infective larvae (cercariae). Cercariae are released by intermediate snail hosts. There are three major species: *Schistosoma mansoni*, endemic to Africa, the Eastern Mediterranean, the Caribbean, and South America; *Schistosoma haematobium*, found in the Middle East and Africa; and *Schistosoma japonicum*, found in China, Indonesia, and the Philippines. Two minor species, *Schistosoma mekongi* and *Schistosoma intercalatum*, have limited distribution in Southeast Asia and Central and West Africa, respectively.

After cercariae penetrate the skin, developing worms migrate to the mesenteric blood vessels (*S. mansoni* and *S. japonicum*) or to the venous system surrounding the ureters, bladder, and reproductive organs (*S. haematobium*). Rarely, adult worms can migrate to the vessels of the spinal cord or brain. More often, host morbidity results from parasite eggs lodging in surrounding host tissues with resultant granulomatous inflammation and scar formation.

CNS disease (neuroschistosomiasis) occurs from either adult worms migrating to the vessels of the spinal cord or brain (very rare) or from aberrant deposition of eggs in the spinal cord or brain, causing inflammation and fibrosis. Patients with schistosomiasis manifest with neurologic symptoms in less than 5 percent of cases, although neuroschistosomiasis may be underdiagnosed.

Cerebral schistosomiasis occurs primarily with *S. japonicum*, followed by *S. haematobium*. *S. mansoni* more commonly causes spinal cord lesions. As expected, the clinical presentation will be dictated by the location of the eggs and the host immune response. Cerebral disease can present with acute encephalopathy; seizures; headaches; focal motor, sensory, or visual deficits; or cerebral vasculitis. Spinal cord disease will present as an acute or subacute myelopathy or myeloradiculopathy and will often involve the cauda equina.

Diagnosis depends on considering neuroschistosomiasis in patients from endemic areas or in those who have traveled to such areas and present with an appropriate neurologic syndrome or imaging and have evidence of a schistosomal infection. Evidence of infection can be garnered through microscopic identification of eggs in stool (*S. japonica* or *S. mansoni*) or urine (*S. haematobium*); antigen detection by ELISA or lateral flow assay in stool, urine, or CSF; or serology (at CDC, some commercial labs) in patients who do not live in endemic countries. Importantly, serology will not help distinguish symptomatic versus asymptomatic coinfection in a patient from an endemic country. Definitive diagnosis is through the demonstration of eggs in neural tissue, but such testing is highly invasive and rarely necessary.

Treatment for neuroschistosomiasis will generally involve corticosteroids and the antihelminth drug praziquantal. Oxamniquine is an alternative to praziquantel but is only effective against *S. mansoni*. In patients with hydrocephalus or cord compression, surgical interventions may also be part of the treatment.[15]

Paragonimiasis

Paragonimus species are endemic in areas of Asia (particularly China and Southeast Asia), sub-Saharan Africa, and South and Central America, and are transmitted through the consumption of raw or undercooked crustaceans. Paragonimiasis transmission has also been documented within the United States, from eating undercooked crawfish in the Midwest (Mississippi River drainage basin). Disease occurs as maturing larvae migrate through host tissues from the gastrointestinal tract to the lungs. Cerebral paragonimiasis is rare and caused by aberrant migration into the brain or, rarely, the spinal cord. Patients can present with an eosinophilic meningitis or meningoencephalitis, encephalopathy, seizures, or focal findings in the case of cerebral disease or a spinal cord syndrome in spinal disease.

Diagnosis depends on a history of exposure, along with parasitologic or serologic (CDC) evidence of infection. Sputum examination for ova can identify the lung fluke *Paragonimus westermani*, but multiple sputum specimens may be needed. Neuroimaging is generally nonspecific and may reveal calcifications (chronic lesions), enhancing or hemorrhagic lesions, and possibly a migration tract. Recommended treatment is corticosteroids and praziquantel.

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CHAPTER

47

Chronic Meningitis

PRASHANTH S. RAMACHANDRAN ■ MICHAEL R. WILSON

DEFINITION
APPROACH
INFECTIOUS CAUSES OF CHRONIC MENINGITIS
- *Cryptococcus* Species
  - *Risk Factors*
  - *Presentation*
  - *Diagnostic Testing*
  - *Treatment*
- *Aspergillus fumigatus*
  - *Risk Factors*
  - *Presentation*
  - *Diagnostic Testing*
  - *Treatment*
- *Candida* Species
  - *Risk Factors*
  - *Presentation*
  - *Diagnostic Testing*
  - *Treatment*
- *Mycobacterium tuberculosis*
  - *Risk Factors*
  - *Presentation*
  - *Diagnostic Testing*
  - *Treatment*
- Neuroborreliosis (Lyme) Disease
  - *Risk Factors*
  - *Presentation*
  - *Diagnostic Testing*
  - *Treatment*
- Neurosyphilis
  - *Risk Factors*
  - *Presentation*
  - *Diagnostic Testing*
  - *Treatment*
- Neurocysticercosis
  - *Risk Factors*
  - *Presentation*
  - *Diagnostic Testing*
  - *Treatment*
- Viral Etiologies

INFLAMMATORY CAUSES OF CHRONIC AND RECURRENT MENINGITIS
- Neurosarcoidosis
  - *Risk Factors*
  - *Presentation*
  - *Diagnostic Testing*
  - *Treatment*
- Primary Central Nervous System Vasculitis
  - *Risk Factors*
  - *Presentation*
  - *Diagnostic Testing*
  - *Treatment*
- Rheumatoid Arthritis
  - *Risk Factors*
  - *Presentation*
  - *Diagnostic Testing*
  - *Treatment*
- IgG4-Related Disease
  - *Risk Factors*
  - *Presentation*
  - *Diagnostic Testing*
  - *Treatment*
- Malignancy
  - *Risk Factors*
  - *Presentation*
  - *Diagnostic Testing*
  - *Treatment*

DRUG-INDUCED MENINGITIS
RECURRENT MENINGITIS
CONCLUDING COMMENTS

Chronic meningitis is a challenging condition in which the etiology often eludes the treating physician. There are a multitude of potential causes that span several specialties, sometimes leading to input from colleagues in neurology, internal medicine, infectious diseases, rheumatology, immunology, and oncology (Table 47-1). A meticulous approach to the history, exam, and ordering of correct investigations may help lead to the diagnosis

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TABLE 47-1 ■ Differential Diagnosis of Chronic Leptomeningeal Enhancement

Infection
Viral meningitis
Spirochetal infections: syphilis, Lyme disease, neuroleptospirosis
Basilar predominant: listeriosis, tuberculous meningitis, endemic fungi, neurocysticercosis, amoebic meningitis
Autoimmune/Inflammatory
Neurosarcoidosis
Behçet disease
Vogt–Koyanagi–Harada syndrome and other uveomeningitis syndromes
IgG4-related disorders
Histiocytosis
Primary CNS vasculitis
Neuropsychiatric systemic lupus erythematosus
Monogenic autoinflammatory disorders
Neoplasm
Leptomeningeal carcinomatosis
Diffuse leptomeningeal glioneuronal tumor
Lymphoma
Chemical/Toxic
NSAIDs
IVIg
Antimicrobials (e.g., trimethoprim/sulfamethoxazole)
Immunosuppressants and chemotherapeutics
Anticonvulsants (e.g., lamotrigine, carbamazepine)
Neurosurgical procedures
Ruptured dermoid cyst

IgG4, immunoglobulin G4; CNS, central nervous system; NSAID, nonsteroidal anti-inflammatory drug; IVIg, intravenous immunoglobulin.
Adapted from Table 3-3 in Continuum (Minneap Minn) 24:1298, 2018.

and prompt treatment of these patients. This chapter outlines an approach to the patient with chronic meningitis along with some pearls and clues that may aid in the diagnosis of particularly common and important causes of chronic meningitis. Other chapters that contain more detailed discussions of particular disorders are highlighted throughout.

DEFINITION

The meninges are composed of the dura mater, the arachnoid, and the inner most layer, the pia mater. The term "meningitis" typically refers to inflammation of the leptomeninges (i.e., the arachnoid and pia mater) and can be detected by a pleocytosis in the cerebral spinal fluid (CSF), enhancement on contrast magnetic resonance imaging (MRI), or through the discovery of inflammatory cells on meningeal biopsy. Meningitis is considered chronic when the CSF pleocytosis, or the symptoms found to be associated with the meningitis, last greater than 1 month. However, the strict definition of 1 month should not dissuade the clinician from considering the differential diagnosis associated with chronic meningitis if there is clearly chronicity to the symptoms. The category of subacute meningitis encompasses almost all of the same etiologic agents as chronic meningitis and frequently progresses to chronic meningitis if not treated. Chronic meningitis symptoms may sometimes wax and wane, making it appear as if the patient is suffering from recurrent attacks of acute meningitis; however, there is usually no resolution of the CSF pleocytosis in between these attacks. This situation differs from *recurrent meningitis* in which there is a clear resolution of symptoms and CSF pleocytosis in between symptom worsening.

Pachymeningitis is inflammation of the dura. As this layer of the meninges is not in direct contact with the CSF space, which lies between the arachnoid and pia, CSF pleocytosis is rare unless there is also leptomeningeal involvement. Pachymeningitis is diagnosed based on neuroimaging and sometimes meningeal biopsy; its differential diagnosis is distinct from chronic leptomeningitis (Table 47-2).

APPROACH

Since there are a multitude of causes of chronic meningitis it is important to take a systematic approach to evaluating these patients. There are three broad categories of disease that cause chronic meningitis: infectious, autoimmune, and neoplastic. In addition, clinicians should carefully screen the medication list for compounds that are known to cause a chemical meningitis. It is not recommended that the clinician test for every possible etiology on the first consultation. Rather, systematically thinking through the entire array of causes and querying whether they are more or less likely based on the history, physical exam, neuroimaging, and initial CSF studies will help narrow down which specific diagnostic tests will be most high yield.

A great deal of information and possible clues can be elicited from the history and examination. An extensive history centered on exposures to possible infections

TABLE 47-2 ■ Differential Diagnosis of Chronic Pachymeningeal Enhancement

Infection
Mycobacterium species
Syphilis
Lyme disease
Viral meningitis (HTLV-1, herpes viruses)
Fungal meningitis
Primary amoebic meningitis
Autoimmune/Inflammatory
Neurosarcoidosis
Rheumatoid arthritis
Sjögren syndrome
Vogt–Koyanagi–Harada syndrome and other uveomeningitis syndromes
IgG4-related disorders
Histiocytosis
Granulomatosis with polyangiitis
Neoplasm
Leptomeningeal carcinomatosis
Glioneuronal tumor
Lymphoma
Focal pachymeningeal enhancement: meningioma, calvarial lesions
Iatrogenic
Lumbar puncture
Shunt placement
Craniotomy
Intrathecal chemotherapy
Other
Spontaneous intracranial hypotension due to trauma, connective tissue disorder, transdural spinal osteophytes, CSF venous fistula or Gorham–Stout disease[1]
Venous sinus thrombosis
Extramedullary hematopoiesis
Postsubarachnoid hemorrhage
Idiopathic

HTLV, human T-cell leukemia virus; IgG4, immunoglobulin G4.
Adapted from Table 3-2 in Continuum (Minneap Minn) 24:1298, 2018.

(e.g., travel, animal exposures, tick and mosquito bites, intravenous drug use, occupational exposures) must be performed. A detailed history probing for evidence of autoimmune disease or other systemic disorders that may be related to chronic meningitis should be taken, as well as a thorough review of both prescription and over-the-counter medications. A prior history of any systemic malignancy, both active and in remission, may prompt the suspicion of metastatic disease to the meninges while also recognizing that leptomeningeal carcinomatosis can be the presenting syndrome of a previously undiagnosed systemic cancer. Neuroimaging features, best captured by MRI with and without contrast of the brain (and often the spinal cord), and the basic CSF profile (i.e., cell count and differential, glucose, protein) can also help to narrow the list of potential causes.

Given the weeks- or months-long investigations that are often performed to identify a chronic meningitis etiology, it is important to systematically track all results and pending investigations. It is also important to understand the specificity and sensitivity of the tests ordered to avoid misdiagnoses. Early in the investigation, consideration should be given to the utilization of wide-ranging polymerase chain reaction (PCR) assays for bacteria or fungi or even more agnostic, hypothesis-free diagnostic testing with metagenomic next-generation sequencing, to comprehensively screen for the whole range of infectious etiologies.[2] These broad tests can increasingly provide quick and actionable results that avoid a long and arduous journey with multiple investigations. Occasionally a meningeal biopsy is needed to make the diagnosis. Whole-body imaging through CT, PET, or both can sometimes identify peripheral sites of inflammation that might be amenable to biopsy rather than a more invasive biopsy of the central nervous system (CNS).

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

Infectious causes of chronic meningitis include fungal, atypical bacterial, viral, and parasitic disorders. It is critical to assess the patient for an immunocompromised state, helping to narrow down the most likely organisms responsible. However, many infectious causes of chronic meningitis can occur in immunocompetent patients, and a normal immune system should not dissuade the physician from an infectious cause. A detailed social history is also critical, including travel history, occupational history, sick contacts, animal contacts, and drug abuse history.

Cryptococcus Species

Fungal infections that can occur in immunocompetent patients include *Cryptococcus* species, *Candida* species (e.g., following neurosurgical interventions or in those with an injection drug use history), *Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis,* and *Sporothrix schenkii. Cryptococcus neoformans, Candida* species, and *Aspergillus* species should be considered in immunocompromised patients.

Certain fungi are endemic to specific regions in the United States. *C. immitis* is predominantly located in the Southwest; *H. capsulatum* in the central, southeastern, and mid-Atlantic states; *B. dermatitidis* is primarily located along the Ohio and Mississippi Rivers and Great Lakes; and *C. gattii* has usually been seen in the Pacific Northwest and in the southeastern United States.[3] A more extensive discussion of fungal infections and their neurologic manifestations other than chronic meningitis can be found in Chapter 45.

Cryptococcus species are yeast-forming organisms. There are two major types that are neuroinvasive: *C. neoformans* and *C. gattii. C. neoformans* is the major cause of cryptococcal meningitis in immunocompromised patients (including the elderly), whereas *C. gattii* can cause infection even in immunocompetent patients.[4] The yeast is an intracellular pathogen that infects macrophages.

RISK FACTORS

Cryptococcus often causes opportunistic infection in human immunodeficiency virus (HIV)–infected patients. As a result of the high prevalence of HIV, cryptococcal meningitis is the most common cause of subacute and chronic meningitis in sub-Saharan Africa. Any form of significant immunosuppression, specifically T-cell-mediated immunosuppression, can lead to a propensity for cryptococcal meningitis. *C. neoformans* can be contracted from pigeon droppings. *C. gattii* is found in red gum trees and soil, and it is endemic in tropical and subtropical regions throughout the world *C. gattii* can cause infections in immunocompetent individuals.

PRESENTATION

Cryptococcal meningitis presents with insidious, progressive, subacute-to-chronic meningitis. Patients can present with a basilar meningitis with cranial nerve entrapment. The encapsulated yeast forms frequently block the arachnoid granules and CSF reabsorption, leading to very elevated intracranial pressures. Even in patients taking antifungal therapy, elevated intracranial pressure is a frequent cause of mortality if frequent therapeutic lumbar punctures are not performed. Elevated intracranial pressures in cryptococcal meningitis can manifest with headache, hydrocephalus, papilledema, unilateral or bilateral VIth nerve palsies, and progressive coma. In addition to symptoms of meningitis, patients can present with cryptococcomas in the brain parenchyma (most frequently in the basal ganglia) leading to focal neurologic signs and symptoms. HIV-infected patients with low CD4 counts can present with cryptococcemia, and pulmonary and ocular cryptococcal infections can also occur.

DIAGNOSTIC TESTING

CSF typically displays a lymphocytic pleocytosis with low glucose and elevated protein but can be bland in severely immunocompromised patients in whom the index of suspicion must remain very high. Opening pressures are generally elevated. In HIV-infected patients, the cryptococcal antigen (CrAg) test is very sensitive (98%) and specific (99%). It can be performed as a bedside lateral flow assay and is the test of choice for the diagnosis of cryptococcal meningitis. The CrAg can remain positive in the CSF for years despite successful treatment, and therefore, it is not recommended as a follow-up test to assess for treatment success or failure. Fungal cultures may detect cases of low fungal burden that are CrAg negative.

On MRI, patients may display leptomeningeal enhancement, although in highly immunocompromised patients, neuroimaging may be unremarkable. Cryptococcomas can vary in location but have a propensity for the basal ganglia and typically present as enhancing circumscribed lesions.

TREATMENT

Treatment is separated into induction, consolidation, and maintenance phases. Gold standard induction therapy involves intravenous amphotericin B and flucytosine, typically for 2 weeks duration. Oral fluconazole is then used for consolidation and maintenance therapy. In HIV-infected patients not on treatment, initiation of antiretroviral therapy should be delayed until after 4 weeks of antifungal treatment to reduce the risk of the immune reconstitution inflammatory syndrome (IRIS). Adjunctive dexamethasone use in HIV-infected patients is not recommended.

Symptomatic management is critical, especially management of elevated intracranial pressure which may initially require daily lumbar punctures or an extraventricular or lumbar drain. A worsening of neurologic function does not necessarily suggest treatment failure or another pathogen, as it may represent IRIS, especially if worsening occurs 2 to 4 weeks after starting antiretroviral medications.

Aspergillus fumigatus

Aspergillus fumigatus is a mold that is ubiquitous in soil. The fungus releases airborne spores that are inhaled, causing either pulmonary or sinus disease as well as invasive disease in immunocompromised patients. CNS disease occurs through hematologic spread or via direct spread from the contiguous nasal sinuses.

Risk Factors

Individuals at highest risk are those with hematologic malignancies, post-stem cell or solid organ transplant, HIV infection, and chronic granulomatous disease.

Presentation

Presentations can vary, however there is a propensity for associated vasculitis and infarcts, especially involving the basal ganglia. Direct CNS invasion can present as a basilar meningitis. Mass lesions (aspergillomas) and abscess formation are common, sometimes manifesting with focal neurologic deficits and seizures.

Patients can have pulmonary or nasal sinus involvement. With hematogenous spread, additional sites by seeding are possible, and ophthalmic manifestations are particularly common, including endophthalmitis.

Diagnostic Testing

The diagnosis of *Aspergillus* can be challenging. Cultures, PCR-based testing, or attempting to biopsy tissue at a non-CNS site is preferable; the lung (via bronchoalveolar lavage) and nasal sinus sampling are the most common sources of tissue. Brain biopsy may be required if a diagnosis cannot be made. CSF testing for galactomannan and 1,3-β-D-glucan are antigen assays that assess for components of the fungal cell wall, carrying sensitivities of 70 and 85 percent, respectively.

Radiologic presentations include basilar or diffuse leptomeningeal enhancement, aspergillomas, abscess formation, and vasculitis with infarctions and hemorrhages. A high-resolution thin-slice CT scan of the sinuses may demonstrate a breech in the bone allowing for, or the result of, direct fungal invasion. Contrast enhancement of the dura in a similar region on MRI may represent direct spread.

Treatment

Voriconazole is the mainstay of treatment for invasive *Aspergillus* therapy; however, the condition still carries a high mortality rate despite optimal treatment.

Candida Species

Candida albicans is a yeast that is a commensal organism found commonly in mucosal regions of the body. Disruption to the regional microbiome or immunosuppression can lead to overgrowth and disease by this and other *Candida* species. Invasive *Candida* infections are spread hematogenously and can seed multiple areas, including the CNS.

Risk Factors

Risk factors include hematologic and solid organ malignancies, significant immunosuppression, prolonged ICU stay with invasive instrumentation, broad-spectrum antibiotics or antifungals, and organ failure. Intravenous drug use is also a risk factor for all *Candida* species, either from skin flora being introduced intravenously, poor injecting habits (licking the needle before use), or from lemon juice used to break down impure heroin (generally leading to *C. albicans*).

Presentation

A presentation of acute-to-chronic meningitis is common. Vasculitis presenting with ischemic or hemorrhagic strokes is less common. Subarachnoid cysts causing a compressive myelopathy have also been reported.

Due to hematogenous spread, *Candida* can seed systemically to multiple locations including the skin and the heart. Infectious endocarditis can serve as an ongoing source of infectious emboli. Endophthalmitis commonly occurs, and all patients with fungemia or CNS disease should undergo a thorough ophthalmologic examination.

Diagnostic Testing

Definitive diagnosis through blood cultures, vitreous, bone, or skin biopsies is preferable to a brain biopsy if there are indications of systemic involvement. The CSF displays a similar profile to other fungal infections although a neutrophilic pleocytosis is sometimes possible. Fungal cultures are helpful in growing the organism. 1,3-β-D-Glucan is a component of the *Candida* cell wall and can be a sensitive assay for *Candida* spp. when tested in the CSF.

Leptomeningeal enhancement and microabscess formation can be seen on neuroimaging. Cases of ventriculitis, either from direct neurosurgical intervention from an external ventricular device or via hematogenous spread has been reported. Mycotic aneurysm formation and vasculitis can occur from infectious emboli, often in the setting of endocarditis. Loculated cysts in the subarachnoid space can rarely be seen.

TREATMENT

The treatment of CNS candidal infection is intravenous amphotericin B with or without flucytosine, although because of the common development of drug resistance, combination antifungal therapy is now favored. Fluconazole is frequently used as a long-term maintenance therapy.

Mycobacterium tuberculosis

Mycobacterium tuberculosis is an acid-fast, slow-growing, aerobic bacterium that spreads mainly through the air. Pulmonary tuberculosis (TB) is the most common manifestation, with only 1 to 5 percent of cases involving extrapulmonary sites, including approximately 100,000 cases of TB meningitis per year. TB meningitis carries a high morbidity and mortality if not treated early.[5] Further discussion of the many neurologic presentations of TB can be found in Chapter 40.

RISK FACTORS

Pulmonary TB risk factors include time spent in an endemic region, close contact with a person with active TB, groups with high rates of infection including homeless persons, HIV-infected persons, those who use intravenous drugs, and persons who reside in correctional facilities, nursing homes, and homeless shelters. Immunosuppression with HIV is a major risk factor for disseminated disease and TB meningitis. TNF-α inhibitors and long-term steroid use can lead to TB reactivation.

PRESENTATION

Patients generally present in a subacute manner with constitutional symptoms and progressive meningismus for greater than 1 week. Basilar meningitis is the classic presentation for TB meningitis; however, there can be multiple other manifestations involving the leptomeninges and pachymeninges. Secondary vasculitis and arachnoiditis can lead to strokes and cranial nerve palsies due to compression and inflammation of the vessels and nerves as they traverse the subarachnoid space. Tuberculomas can lead to focal neurologic signs and mass effect. Hydrocephalus and raised intracranial pressure can progress to coma and death.

Only 50 percent of patients with TB meningitis will have an abnormal chest x-ray. On more detailed systemic imaging, extrapulmonary TB may be evident with regions of prominent lymphadenopathy, including the abdomen.

DIAGNOSTIC TESTING

Diagnosis is notoriously difficult due to the paucibacillary nature of the disease. CSF typically displays a lymphocytic or neutrophilic pleocytosis with low glucose and elevated protein, but can be relatively bland in severely immunocompromised patients in whom the index of suspicion must remain very high. The automated PCR assay (GeneXpert MTB/RIF Ultra) is currently the single most sensitive and specific CSF assay for diagnosing TB meningitis, but it will still fail to identify at least 30 percent of clinically-suspected cases. Diagnosis from pulmonary sites or other extrapulmonary regions is helpful, and therefore systemic imaging and biopsy should be considered early in the work-up. A negative PPD or IFN-γ release assay does not rule out the disease. Cultures take 4 to 8 weeks to grow and are therefore used mainly as a retrospective diagnosis. TB is a reportable disease in most jurisdictions with implications for close contacts of the patient including exposed healthcare workers.

Enhancement along the basilar meninges is the most common radiologic finding followed by hydrocephalus. Posterior circulation and basal ganglia strokes may occur from vasculitis. Mycotic aneurysms can be evident later in the disease process. Although leptomeningitis is more common, TB meningitis can also lead to pachymeningitis.

TREATMENT

Empiric treatment is often started even with negative TB testing if clinical suspicion remains high. First-line therapy is a combination of rifampicin, isoniazid, pyrazinamide, and ethambutol. Steroids are given concomitantly when antimicrobial therapy is initiated to prevent paradoxical clinical worsening. Clinical improvement that wanes after these adjunctive steroids are discontinued should prompt the physician to consider paradoxical clinical worsening, multidrug-resistant TB, and alternative infectious and noninfectious meningitis etiologies that may have symptomatically improved with glucocorticoids. Ongoing supportive care is critical to detect and manage the many potential neurologic sequelae which may result from TB meningitis including raised intracranial pressures, strokes, IRIS, and hyponatremia.

Neuroborreliosis (Lyme) Disease

Lyme disease is caused primarily by the bacterium *Borrelia burgdorferi*, a spirochete transmitted by the *Ixodes scapularis* tick in North America and Europe (see Chapter 39 for further details).

RISK FACTORS

Exposure in endemic regions is the major risk factor for the disease, mainly in the east coast of the United States and Europe, although *B. burgdorferi* continues to spread throughout North America with an increased geographic range of its tick host.

PRESENTATION

Chronic meningitis with cranial nerve abnormalities is one of the most common presentations of neurologic Lyme disease. Bannwarth syndrome is a lymphocytic meningoradiculitis with painful radiculopathies that is an uncommon presentation in the United States.

The classic bullseye rash may not be recalled by patients or may be missed in around 30 percent of patients. Fevers, fatigue, arthralgias, and myocarditis can occur as the disease progresses. Neurologic manifestations can occur early in the disease course or be a more delayed presentation.

DIAGNOSTIC TESTING

Neurologic Lyme disease always has a CSF pleocytosis (usually lymphocytic) that will resolve with treatment. CDC criteria suggest the two-tier ELISA test followed by a confirmatory Western blot since the *B. burgdorferi* PCR is insensitive. The duration of illness is an important factor which relates to the number of bands that must be positive to meet criteria. A positive IgM alone is not enough for a diagnosis, and conversion to IgG is required. As neurologic Lyme disease can present early in the disease course, the IgG antibody may be negative, and patients living in an endemic area with a characteristic rash can be treated presumptively. An elevated IgG Lyme antibody index is diagnostic of neurologic Lyme infection. *B. burgdorferi* antibodies (including IgM) can remain elevated in the CSF despite therapy for up to a year and should not be used to monitor treatment effect.

MRI may show leptomeningeal and cranial nerve enhancement in addition to nonspecific white matter–predominant T2 hyperintensities in the brain and spinal cord.

TREATMENT

Although 14 days of parenteral ceftriaxone is standard of care for neurologic Lyme disease in the United States, European data suggest that doxycycline 200 mg twice daily for 14 days is equally as effective.

Neurosyphilis

Treponema pallidum is a spirochete, whose infection leads to syphilis, a sexually transmitted disease. Syphilis infection can be divided into primary, secondary, and tertiary stages, and neurosyphilis can occur during any stage of the disease.[6] HIV coinfection can accelerate disease progression and increases the risk of neuroinvasive disease.

RISK FACTORS

There is currently a worldwide epidemic of syphilis. Those with HIV infection, men who have sex with men, and persons with a serum titer rapid plasma reagent (RPR) titer greater than 1:32 have an increased risk of developing neurosyphilis. No prior treatment or incomplete treatment for syphilis should also increase suspicion for neurosyphilis.

PRESENTATION

Classic neurosyphilis presentations include meningitis, meningovascular disease with multiple strokes, otic and ocular forms, tabes dorsalis, and a syndrome of progressive cognitive deficits called general paresis. Chronic meningitis manifests with meningeal symptoms as well as cranial neuropathies (including optic neuropathy and hearing loss) and often culminates with a vasculitis of small and medium-sized vessels with associated strokes. A progressive myelopathy, tabes dorsalis, can occur during this stage as well. Further discussion can be found in Chapter 39.

Systemic symptoms are common with syphilis. A syphilitic chancre is only noted in around 30 percent of patients and presents with a nonpainful ulcer. Secondary syphilis is characterized by a pustular rash, fevers, and lymphadenopathy. Tertiary syphilis is associated with syphilitic aortitis and systemic gumma.

DIAGNOSTIC TESTING

A patient cannot have neurosyphilis if their serum *T. pallidum* particle agglutination assay (TPPA) test is negative. Thus, the serum TPPA is a quick rule-out test for the condition and should be sent in most neurologic presentations. The 2018 CDC diagnostic criteria for definite neurosyphilis require both a positive serum treponemal (TPPA, fluorescent treponemal antibody absorption antibody) and nontreponemal test (RPR; venereal disease research laboratory or VDRL) with a positive CSF VDRL. There is generally a CSF lymphocytic pleocytosis, but the diagnostic criteria do not require this feature if the CSF protein is elevated. A negative CSF VDRL does not rule out the disease as the assay only has a 70 percent sensitivity; if the CSF profile is abnormal, the patient may still warrant treatment as having "probable" neurosyphilis. Syphilis is a reportable disease.

Leptomeningeal enhancement is seen on MRI during the meningitis stage. Cranial nerve enhancement may be visible. Syphilitic gumma can resemble meningiomas when they are attached to the dura.

TREATMENT

Treatment is with aqueous crystalline penicillin G 3 to 4 million units every 4 hours for 10 to 14 days. In the United Kingdom and Australia, 40 to 60 mg of prednisolone is given for 3 days, with the first dose prior to the antibiotic infusion, to prevent a Jarisch–Herxheimer reaction, which can lead to an endotoxin-like product-mediated, occasionally dramatic, syndrome of fever and rash that lasts from hours to days.

Neurocysticercosis

RISK FACTORS

Residence in, or travel to, regions that are endemic with *Taenia solium* should lead to consideration of neurocysticercosis as a cause of chronic meningitis. The infection occurs in areas with poor sanitation and where pigs roam freely with humans. However, because *T. solium* spreads by the fecal-oral route, transmission can still occur amongst close contacts in nonendemic settings. See Chapter 46 for further details.

PRESENTATION

Neurocysticercosis can have an asymptomatic presentation in a large proportion of patients with parenchymal cysts being discovered incidentally on brain imaging done for another reason. The most common presentation is seizure after a cyst is recognized by the immune system and begins to degenerate and swell. Subarachnoid neurocysticercosis is the form of the disease that leads to chronic meningitis; it can have a variety of complications ranging from headaches secondary to obstructive hydrocephalus from ventricular cysts, nuchal rigidity, radiculopathies and cranial neuropathies secondary to nerve inflammation or compression by subarachnoid cysts, arachnoiditis, and vasculitis. Patients are typically afebrile and systemically well.

DIAGNOSTIC TESTING

The CSF displays a pleocytosis with a variable cell differential that may or may not include eosinophils. Hypoglycorrhachia can be seen. The cysticercal antigen and antibody tests are very sensitive in patients with subarachnoid disease with the former assay being much more useful for identifying active disease in a patient from an endemic area.

CT scans frequently show scattered small calcifications from degenerated parenchymal cysts. MRI of the brain in active disease reveals well-demarcated parenchymal cysts with a scolex in the center that may or may not have rim enhancement or surrounding edema. Patients with chronic meningitis and subarachnoid disease can present with a basilar meningitis and subarachnoid cysts that appear anywhere along the neuroaxis. Intraventricular cysts can account for dynamic and acute obstructive hydrocephalus that can be treated by surgical cyst removal or ventriculoperitoneal shunting. Intraventricular cysts can be difficult to visualize, and if there is a clinical suspicion, additional MR sequences such as fast imaging employing steady-state acquisition can more easily detect their thin walls. Two-thirds of patients with subarachnoid disease will have cysts along the spinal cord even without signs or symptoms of myelopathy or radiculopathy.

TREATMENT

Subarachnoid disease is very difficult to treat and requires long-term management and surveillance. Guidelines suggest albendazole (15 mg/kg per day) and concurrent praziquantel (50 mg/kg per day) until there is resolution of imaging abnormalities and improvement of CSF parameters including decreasing CSF pleocytosis and, ideally, negative CSF antigen testing. Steroids are given prior to commencement of antiparasitic medications and then intermittently throughout the chronic treatment course to manage recurrent flares of meningitis.

Before initiating therapy, patients should undergo an ophthalmologic examination to rule out intraocular infection that might require surgery. Consideration should be given to screening for latent TB as well as strongyloidiasis. Because serologies for strongyloides can have a slow turnaround time in the laboratory, empiric treatment with ivermectin is reasonable for patients who come from endemic areas. Methotrexate can be used as a steroid-sparing agent in cysticercosis patients, and there is recent evidence for the utility of TNF-α inhibitors as alternate steroid-sparing agents. Members of the patient's household and family should be screened with stool ova and parasite examinations to help limit spread of the disease.

Viral Etiologies

While viruses play a major role in the etiology of acute meningitis, chronic CNS viral infections are uncommon and typically present with both a meningitis and a parenchymal component so that patients more accurately are classified as having a chronic meningoencephalitis or meningomyelitis. Chronic viral causes of meningoencephalitis in immunocompetent patients include measles virus causing subacute sclerosing panencephalitis and various herpes viruses including varicella zoster virus. In severely immunosuppressed patients, HIV-1, herpes viruses (e.g., varicella zoster virus, Epstein–Barr virus, and cytomegalovirus), enteroviruses, orthobunyaviruses, polyomaviruses including JC virus (causing progressive multifocal leukoencephalopathy), and a variety of other very rare viral infections can occur. Human T-lymphotropic virus type 1 (HTLV) is an important cause of chronic meningomyelitis in immunocompetent individuals from endemic parts of the world that leads to tropical spastic paraparesis.

INFLAMMATORY CAUSES OF CHRONIC AND RECURRENT MENINGITIS

Neurosarcoidosis

Sarcoid is an autoimmune systemic granulomatous disease process characterized by noncaseating granulomas (see Chapter 49). Although initially thought to be incited by an unknown pathogen, it has become clearer over the last few decades that the disease is likely a primary autoimmune condition with specific HLA and other genetic associations. Diagnosis can be difficult, and infectious and other causes of chronic meningitis need to be carefully ruled out.

RISK FACTORS

African American and Scandinavian populations have a higher incidence of sarcoidosis. Women also have a somewhat higher incidence of the disease than men.

PRESENTATION

Neurologic manifestations can predate systemic manifestations in up to 30 percent of neurosarcoidosis cases. Chronic meningitis, mass-like lesions, pituitary involvement, cranial nerve involvement (specifically optic and facial), and myelopathy are common presentations. Vasculitis is a rare manifestation. Neurosarcoidosis tends to be localized to one region of the nervous system with relapses occurring in the same region in an individual patient. There can be a predilection for the basilar meninges. At onset especially, there is generally a clinical–radiologic dissociation with the patient appearing significantly more well than the disease burden on neuroimaging would suggest.

Pulmonary sarcoid is the most common systemic disease manifestation, often featuring hilar lymph node involvement. Cardiac, liver, spleen, skin, and ocular involvement can also occur. Bilateral parotid involvement, uveitis, and bilateral facial nerve involvement are termed Heerfordt syndrome and occur mainly in Scandinavian populations. Erythema nodosum can occur on the lower limbs. Constitutional symptoms of fevers, night sweats, and weight loss may or may not be present.

DIAGNOSTIC TESTING

Histologic review of pathologic tissue, the only true diagnostic test for neurosarcoidosis, shows non-necrotizing, noncaseating granulomas that are well formed. Biopsy-proven sarcoid from brain or leptomeningeal tissue is considered definite neurosarcoidosis. Neurologic manifestations, but with tissue confirmation only from peripheral sites, is classified as probable neurosarcoidosis.[7] Serum and CSF angiotensin-converting enzyme levels are not useful tests in the work-up or management of neurosarcoidosis. When concerns are raised for neurosarcoidosis with no prior history of systemic sarcoid, a whole-body PET scan is useful to look for hypermetabolic lymphadenopathy or other organ involvement in order to identify biopsy targets. Blind biopsies of muscle or conjunctiva have a low yield. A pleocytosis is typically present and may be lymphocytic or neutrophilic. Low CSF glucose and unique oligoclonal bands are seen in approximately 30 percent of cases. If CSF glucose is extremely low, then an alternate diagnosis should be sought.

On neuroimaging, the meninges or dura may appear inflamed with adjacent parenchymal involvement, with an appearance suggesting an "outside to in" process of inflammation. Persistent contrast enhancement, sometimes for months or years, is highly suggestive of neurosarcoidosis. Sarcoid myelopathy may resemble a longitudinally extensive transverse myelitis, but unlike neuromyelitis optica, nodular leptomeningeal enhancement may be seen.

TREATMENT

Neurosarcoidosis is typically steroid responsive. There can be difficulty weaning steroids due to the recurrence of meningitis or parenchymal inflammation. Steroid-sparing agents such as methotrexate, azathioprine, or mycophenolate mofetil are frequently used; recent data suggest that infliximab, a TNF-α inhibitor, can also be highly efficacious.[8]

Primary Central Nervous System Vasculitis

RISK FACTORS

There are no specific risk factors for primary CNS vasculitis, which is a rare and poorly understood entity discussed further in Chapter 50. The disorder typically involves small vessels of the brain and is distinct from systemic vasculitis syndromes such as ANCA-associated vasculitis that can also have CNS involvement.[9] Since secondary CNS vasculitis can also occur as a result of chronic infectious processes, including syphilis, varicella zoster virus, fungal infections, neurocysticercosis, amoebic infections, and TB, a careful exclusion of these entities is important in the work-up of CNS vasculitis.

PRESENTATION

The neurologic presentation of primary CNS vasculitis is incredibly varied and depends on the location of the vasculitis, the vessel size affected, and the specific areas of brain parenchyma at risk of ischemia. Although large-vessel vasculitides may present with a large territory stroke, vessel wall narrowing, and beading, the more common small-vessel involvement seen in primary CNS vasculitis manifests often as persistently contrast-enhancing lesions, including in the spinal cord, along with mass lesions in the brain and chronic leptomeningitis or pachymeningitis.

A thorough search for other causes of systemic vasculitis should be performed in suspected primary CNS vasculitis. Typically, in primary CNS vasculitis all specific and general markers of systemic inflammation are normal. ANCA-negative systemic vasculitis is difficult to diagnose, and an angiogram of peripheral sites (e.g., an abdominal angiogram in polyarteritis nodosum) may be required. Hepatitis B and C viruses should be screened to evaluate for the risk of cryoglobulinemia. Constitutional symptoms of fever, weight loss, and night sweats may indicate a systemic vasculitis with CNS involvement. An ophthalmologic examination is important to assess for ocular involvement.

DIAGNOSTIC TESTING

Leptomeningeal and brain biopsy is the mainstay of diagnosis. The three major pathologic subtypes include those featuring granulomas with multinucleated cells, cases with a lymphocytic predominance, and those demonstrating a necrotizing vasculitis.

Primary CNS vasculitis typically involves vessels whose diameter is difficult to image even with a formal angiography, and therefore normal vessel imaging does not rule out the disorder. Patients with primary CNS vasculitis can have scattered areas of persistently enhancing leptomeninges or parenchymal lesions in the brain or spinal cord seen on neuroimaging. Diffusion restriction and bloom artifact within the lesion may be found on DWI and SWI sequences, respectively.

TREATMENT

Based on treatments for systemic vasculitides, steroids and cyclophosphamide have long been the mainstay for the treatment for primary CNS vasculitis. However, rituximab is becoming more commonly used as an alternative to cyclophosphamide. Tocilizumab, an anti-interleukin-6 monoclonal antibody, has been shown to be effective for temporal arteritis and may have benefit for CNS vasculitis as well.

Rheumatoid Arthritis

RISK FACTORS

Development of rheumatoid arthritis is likely related to both genetic and environmental factors. Older age, female sex, family history, and smoking are risk factors. The development of CNS disease generally occurs in poorly controlled or severe disease and can occur during any stage of the disorder (see Chapter 50 for additional discussion).

PRESENTATION

Patients may present neurologically with leptomeningeal involvement, pachymeningitis, neuropsychiatric manifestations, and focal neurologic signs.

Rheumatoid arthritis is a symmetric, small-joint, inflammatory arthritis with extra-articular manifestations throughout multiple organ systems. Extra-articular manifestations are manifestations of moderate-to-severe disease and can occur during any stage of the disease.

DIAGNOSTIC TESTING

CSF may display a pleocytosis with a normal glucose. CSF anticyclic citrullinated peptide may be elevated in the serum as may rheumatoid factor. Rheumatoid meningitis typically involves the pachymeninges. There may be associated vasculitis and infarcts as well as structural abnormalities in the cervical spine seen on imaging associated with rheumatoid arthritis including atlanto-axial instability, cranial settling, or subaxial subluxation.

TREATMENT

High-dose steroids with a rheumatoid arthritis disease-modifying agent such as a TNF-α inhibitor or B-cell depleting therapy with rituximab may be beneficial for neurologic manifestations of the disorder.

IgG4-Related Disease

RISK FACTORS

IgG4-related disease is a recently recognized entity requiring a tissue diagnosis and a high degree of clinical suspicion. It is a systemic inflammatory disorder with dense infiltration of IgG4-positive plasma cells invading affected tissues. It is likely underdiagnosed and, as a result, risk factors for the disease are still being determined. The most common patient demographic is a middle-aged to elderly man.[10]

PRESENTATION

Symptoms associated with compression of various brain and spinal cord structures from IgG4-related pachymeningitis are the most common presentation. Orbital and neuroendocrine abnormalities associated with ocular and pituitary gland and stalk involvement, respectively, have been reported. Involvement affecting the orbit can result in multiple cranial neuropathies or compromise of the extraocular muscles from mass effect. Patients can have systemic manifestations of IgG4-related disease, but isolated CNS disease is common.

Pancreatitis was the first organ implicated in IgG4-related disease, but like neurosarcoidosis, it is now recognized to affect more than a dozen organ systems, including the thyroid, lungs, kidney, liver, and gall bladder.

DIAGNOSTIC TESTING

Although patients can have a normal CSF profile, a predominantly lymphocytic, mild pleocytosis is not uncommon with an elevated protein and unique oligoclonal bands. Unlike other neuroinflammatory diseases in which IgG4-predominant antibodies are thought to be pathogenic (e.g., chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, autoimmune encephalitis associated with leucine-rich glioma inactivated 1 antibodies), IgG4-related disease does not appear to be autoantibody mediated. Patients may have normal or mildly increased serum IgG4 concentrations, and therefore meningeal biopsy is the primary diagnostic test. Since immunohistochemical staining is not standard for IgG- and IgG4-expressing plasmablasts, the treating physician may need to express the clinical suspicion to the pathologist.

IgG4-related disease can present on neuroimaging as a mass lesion in the pachymeninges (although isolated cases of leptomeningitis have been reported) or the pituitary gland. Less commonly, brain parenchymal or peripheral nerve masses are seen. The pachymeningitis observed is typically smoothly enhancing, with a hypertrophic or nodular appearance.

TREATMENT

Glucocorticoids are the mainstay of treatment with an emerging emphasis on B-cell depleting strategies like rituximab.

Malignancy

RISK FACTORS

Risk factors for leptomeningeal carcinomatosis mirror the risk factors for developing the wide variety of systemic malignancies that, in around 5 percent of cases, can present with, or later be complicated by, disseminated CNS disease. Lymphoma is also an important consideration, with Epstein–Barr virus infection being a special risk factor for CNS lymphoma in HIV-infected patients. Further discussion can be found in Chapter 26.

PRESENTATION

Patients typically experience an insidious onset of some combination of headache, nausea and vomiting, and altered mental status due to communicating hydrocephalus as well as sometimes multiple cranial neuropathies or radiculopathies.

In addition to typical constitutional symptoms associated with systemic malignancies such as fever, night sweats, and anorexia, systemic manifestations are largely dictated by the primary site of the tumor (e.g., shortness of breath and hemoptysis from lung cancer).

DIAGNOSTIC TESTING

The CSF frequently displays a lymphocytic pleocytosis and elevated protein. The glucose may be depressed. Definitive diagnosis relies on CSF cytology and flow cytometry. In patients for whom there is a high degree of clinical suspicion, three large-volume CSF samples should be sent and examined the same day to avoid the decreasing sensitivity that comes with cell lysis when samples sit overnight.

TREATMENT

Leptomeningeal carcinomatosis is highly morbid, with a life expectancy typically less than 2 to 3 months. In consultation with oncology, there may be a role for palliative intrathecal chemotherapy, radiation therapy, or both in addition to ongoing management of the systemic malignancy and its associated complications.

DRUG-INDUCED MENINGITIS

A wide variety of medications can induce a chemical meningitis, and a thorough review of the patient's medications (including supplements and over-the-counter medications) needs to be performed with a special emphasis on recently prescribed medications. Nonsteroidal anti-inflammatory medications (e.g., ibuprofen), intravenous immunoglobulin, immunosuppressant medications, various chemotherapeutics, antiepileptic medications (e.g., carbamazepine and lamotrigine), and antibiotics (e.g., trimethoprim/sulfamethoxazole) can all cause a chronic meningitis. Fortunately, the meningeal irritation typically quickly reverses after cessation of the drug.

RECURRENT MENINGITIS

Some patients with chronic meningitis can appear to have distinct meningitis episodes, but when their CSF is examined in between clinical flares, they are found to have a persistent CSF pleocytosis. There are a small number of disease entities that do cause true recurrent meningitis with interval resolution. The syndrome of recurrent episodes of acute, aseptic meningitis was first described by Pierre Mollaret in the 1940s and was later found to be most commonly secondary to herpes simplex virus type 2 infection.[11,12] In patients with recurrent meningitis, especially those with recurrent fungal, bacterial, and parasitic causes, a thorough immunologic evaluation needs to be performed to evaluate for underlying susceptibility factors. In addition, recurrent CNS bacterial or fungal infections should trigger a careful re-evaluation for potential exposures (e.g., intravenous drug use) as well as for anatomic susceptibilities like skull-base or neural tube defects. A dermoid cyst, or other lesion near the subarachnoid space, that periodically ruptures to cause a recurrent, chemical meningitis may be better visualized on MRI in between meningitis episodes once fluid has reaccumulated in the cyst. Led by the increasing availability of genetic testing, a variety of monogenic autoinflammatory disorders, including TNF receptor associated periodic syndrome (TRAPS) and cryopyrin associated periodic syndrome (CAPS), have been identified that can include chronic and recurrent meningitis as a feature of the syndrome. Particularly for younger patients who lack other obvious risk factors, a consultation with a medical geneticist may be appropriate early in the clinical work-up.

CONCLUDING COMMENTS

Evaluating a patient with chronic meningitis requires a holistic approach to the patient's history and physical examination as well as a wide-ranging consideration of underlying etiologies that span a number of medical subspecialties, especially neurology, infectious diseases, rheumatology, and oncology. A systematic, methodical, and persistent approach to the continuing evaluation of these patients, sometimes over weeks to months, can pay dramatic dividends as many of the responsible etiologies are amenable to treatment. As these evaluations play out over prolonged periods of time, empiric therapies including various antimicrobials and immunosuppressants (especially glucocorticoids) are often given, and transient clinical responses need to be interpreted with caution as some can temporarily mask the underlying etiology and lead the treating physician astray.

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CHAPTER

48

Neurologic Complications of Vaccination

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HISTORIC BACKGROUND
TYPES OF VACCINES
NEUROLOGIC COMPLICATIONS OF VACCINATION
  Possible Mechanisms
  Detection of Vaccine Adverse Events
  Adjuvants and Preservatives
  Smallpox
  Measles, Mumps, and Rubella
    Measles
    Mumps
    Rubella
  Diphtheria, Pertussis, and Tetanus
    Diphtheria
    Pertussis
    Tetanus
  Influenza
  Hepatitis B
  Poliomyelitis
EMERGING VIRUSES
THERAPEUTIC VACCINATION
CONCLUDING COMMENTS

Infectious diseases have historically been the major cause of human morbidity and mortality, and vaccinations have added immeasurably to human health by preventing them. The benefits of vaccinations have not come without some costs, and rare adverse effects of vaccines occur. Many important adverse events are neurologic, and these are discussed in this chapter. The US Centers for Disease Control and Prevention (CDC) regularly update and publish useful summaries of vaccine recommendations.

HISTORIC BACKGROUND

The practice of inoculating microbial agents as a mean to prevent infections was described as early as 200 BCE. Several accounts from the 1500s suggest that smallpox inoculations were common in China and India.[1] In the late 1600s Emperor K'ang Hsi, who had survived smallpox as a child, had his children inoculated. That method involved grinding up smallpox scabs and blowing the matter into the nostril.[2] Inoculation, later called variolation, was introduced to Europe in 1721. This basic strategy of vaccination was employed to generate Louis Pasteur's rabies vaccine, Max Theiler's yellow fever vaccine, and the polio vaccines of Jonas Salk and Albert Sabin.

One of the earliest records of neurologic complications to vaccines was a patient who developed a neuroparalytic syndrome following rabies vaccine around 1889.[3] Since then, several neurologic syndromes have been recognized as occurring in close temporal relationship to vaccination. These complications have had a negative impact on vaccine acceptance, resulting in decreasing vaccination coverage and increases in vaccine-preventable diseases. Given the widespread use of vaccines and the growing concerns about vaccine safety, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) tasked the Institute of Medicine (IOM) to create a Safety Review Committee to evaluate the evidence on possible causal associations between immunizations and certain adverse outcomes. In assessing vaccine safety, the committee performed an examination of the epidemiologic and clinical evidence regarding a possible causal relationship, as well as the possible biologic mechanisms that might support such an association. It also considered the background rates of the disease in the population in

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order to determine legitimate concerns from events that could be temporally related but not caused by the vaccine. The committee released its report in 2012.[4] The findings indicate that measles, mumps, and rubella (MMR), varicella, influenza, hepatitis A, hepatitis B, human papillomavirus, meningococcal, diphtheria toxoid, tetanus toxoid, and acellular pertussis-containing vaccines are safe and that serious adverse events are quite rare. Ongoing efforts continue in order to provide an evidence-based approach to the potential complications of vaccinations.

TYPES OF VACCINES

The underpinning mechanism by which vaccines exert their benefits is by triggering the host's immune system in a way that generates protective immunity against the fully virulent pathogen without causing disease. However, the mechanism of action varies by the type of vaccines (Table 48-1). These include inactivated, attenuated, subunit, conjugate, toxoid, DNA, and vector vaccines.

Inactivated vaccines consist of pathogens that have been treated by chemical or physical methods so that they are nonviable. These treatments generally modify viral proteins essential to some critical function, such as attachment of the virus to the cell. In successful vaccines, these inactivated organisms still have sufficient antigenicity that protective immunity is achieved without the possibility of causing infection. Examples of inactivated vaccines include influenza vaccine, the Salk polio vaccine, rabies vaccine, and the whole-cell pertussis vaccine.

Attenuated vaccines use a virus (or other pathogen) that has been adapted to replicating in a different host system, such as in tissue culture or in chicken eggs. This is achieved by serially passaging the virulent (or wild-type) pathogen in an alternative host system. The pathogen is now "adapted" to the alternative host system and humans become an "unnatural host." The agent is unable to express its full virulence and therefore causes a mild infection while still stimulating full immunity. An example of an attenuated vaccine is the combined MMR vaccine.

Subunit vaccines are composed of subunits of a pathogen that are both nontoxic and immunogenic. They differ from inactivated whole-cell vaccines by containing only the antigenic parts of the pathogen. These parts are necessary to elicit a protective immune response. The older hepatitis B vaccine is an example. That vaccine consisted of a hepatitis B surface antigen that was originally purified from the plasma of hepatitis B carriers. Because of concerns about using human-derived material, the gene for the hepatitis B surface antigen was introduced into yeast that then synthesized

TABLE 48-1 ■ Types of Vaccines Along With a Brief Description of Their Mechanism of Action

Vaccine	Mechanism of Action
Inactivated Influenza Salk polio Rabies Whole-cell pertussis Hepatitis A	Inactivated vaccines consist of pathogens that have been treated by chemical or physical methods so that they are nonviable. Vaccines usually produce a transient antibody response
Attenuated Influenza (nasal) MMR Varicella VZV (Zostavax) Yellow fever Oral polio *Salmonella* (oral) Tuberculosis (BCG)	Pathogens are attenuated by inducing an adaptation to alternative host systems (tissue culture). Thus the agent is unable to express its full virulence in humans and therefore causes a mild infection while still stimulating full immunity
Virus-like particles (VLP) Hepatitis B HPV Chikungunya virus (CHIKV) Influenza (H5N1)	Composed of one or more structural proteins that resemble the structures of viruses and trigger a high humoral and cellular immune response. A key factor regarding VLP safety is the lack of viral genomic material
Recombinant Hepatitis B (Recombivax) HPV (Gardasil) VZV (Shingrix)	Developed by inserting genes from the antigen into a vector, often viruses with low virulence
Conjugate *Haemophilus influenzae*, type b (Hib) (polysaccharide) *Neisseria meningitidis* (polysaccharide conjugate) *Streptococcus pneumoniae*, heptavalent (conjugate polysaccharides) *Salmonella typhi* (capsular polysaccharide)	These vaccines are created by linking polysaccharide antigens to protein carriers, resulting in a robust immunogenic response
Toxoid Diphtheria Tetanus	Toxoid vaccines are made by weakened bacterial toxins. In general they are safe because they cannot cause the disease they prevent and there is no possibility of reversion to virulence. The vaccine antigens are not actively multiplying and do not spread to unimmunized individuals

MMR, measles-mumps-rubella; VZV, varicella zoster virus; HPV, human papillomavirus.

pure hepatitis B surface antigen. Subunit vaccines have also been developed in the hope that immune responses directed at certain antigens, such as Tat, that are expressed very early in the human immunodeficiency virus replication cycle might lead to containment, if not abortion, of infection. Other examples of subunit vaccines include viral envelop proteins, recombinant, and conjugate vaccines.

Viral envelope proteins are noninfectious multiprotein structures that are engineered to self-assemble and form virosomes or "virus-like" particles (VLPs). These virosomes stimulate both cell-mediated and humoral immune responses without triggering the side effects associated with the native virus. VLPs have been used in the human papillomavirus vaccine and hepatitis B vaccine. A recombinant vaccine is a vaccine produced through recombinant DNA technology. This involves inserting the DNA encoding an antigen (such as a bacterial surface protein) that stimulates an immune response into bacterial or mammalian cells, expressing the antigen in these cells, and then purifying it from them.

Conjugate vaccines usually consist of the capsular material of common bacterial pathogens. Antibodies to the capsules allow opsonization of the organism. Examples of component vaccines are those for *Pneumococcus*, *Meningococcus*, and *Haemophilus influenzae* B. These vaccines are often not sufficiently immunogenic in very young infants and have to be specially formulated by conjugation to peptides, which enhances their antigenicity.

Toxoid vaccines are bacterial toxins (e.g., diphtheria, tetanus) that have been rendered nontoxic through chemical treatment, but remain immunogenic.

DNA vaccines are DNA sequences of the gene for an immunogenic antigen that are injected into muscle, where they direct the synthesis of the antigenic peptide. This is then presented to the immune system by the "infected" muscle cell, mimicking a natural infection. DNA vaccines, however, have proved to be poorly immunogenic in humans and none are currently available for human use.

Vector vaccines consist of a nonpathogenic virus that has one of its genes replaced with a gene for an antigen of interest. Such vaccines are being investigated but are not yet available for human use.

More recently, the methods of "reverse vaccinology" have been exploited to make effective vaccines. The process involves sequencing the genome of a target pathogen and scanning for genes that may be useful for vaccines, such as those encoding for virulence factors or surface proteins. These proteins can then be separately expressed and screened for use in animal models, after which human trials can be organized. The advantage of reverse genetic methods is that all of the proteins are available for testing, rather than only an unsuitable subset expressed by a cell line. An example is that of vaccines against meningococcal meningitis, which are protective to all but one serotype, the capsular polysaccharide of which mimics certain neural antigens and is therefore poorly immunogenic.

NEUROLOGIC COMPLICATIONS OF VACCINATION

Possible Mechanisms

Inappropriate immune responses are well-recognized consequences of vaccinations, especially with vaccines made from viruses grown in neural tissue. The classic example is that of the old neurally derived rabies virus, which often resulted in "neuroparalytic accidents" of acute demyelination in either the central or peripheral nervous system. Both acute disseminated encephalomyelitis (ADEM) and Guillain–Barré syndrome (GBS) were observed after the use of these older rabies vaccines and most recently with influenza vaccines.

Two major mechanisms proposed to explain development or activation of autoreactive immune cells after immunizations are molecular mimicry and bystander activation. Molecular mimicry is a process by which antigenic epitopes in the vaccine resemble those in myelin. This structural similarity can result in the development of self-reactive, naïve T and B lymphocytes. Once activated, these cells expand in number and mature into effector T cells leading to pathologic responses mediated by cytokine release and cell-mediated cytotoxicity. Although this mechanism of mimicry has not clearly been shown to act in central demyelination (except possibly for measles, as discussed later), neurally derived vaccines contain myelin antigens themselves (rather than mimics) and therefore can trigger such disease. Peripheral demyelination is known to occur by this mechanism.

Bystander activation is a process by which the activation and expansion of self-reactive lymphocytes is produced by cytokine release and antigenic response to tissue damage. It is conceivable that vaccine antigens could trigger bystander activation just as an infectious agent does.

Detection of Vaccine Adverse Events

Detection of vaccine adverse events can be difficult as they are uncommon and often manifest as illnesses that are known to occur in the unvaccinated. Many of these illnesses are not reportable to health departments. Health officials, however, will take note of an unusually high incidence of disease and launch an investigation. Surveillance for any unusual disease activity can be active or passive. Active surveillance is when cases are actively sought by sending questionnaires to physicians' offices and hospitals or by systematically examining hospital records. Passive surveillance occurs when physicians or the public send unsolicited information about cases to health department officials. Passive surveillance provides very limited epidemiologic information, as it does not indicate the proportion of those with the complication who were actually reported (no numerator information) and how many were actually exposed to the vaccine (no denominator information); furthermore, the clinical details often are insufficient to make a secure diagnosis. The Vaccine Adverse Event Reporting System (VAERS) is a passive surveillance system in which complications are reported to the FDA. Table 48-2 summarizes selected neurologic syndromes reported to VAERS in association with various vaccines. Another passive surveillance system consists of the National Vaccine Injury Compensation Program, which compensates individuals who have had a serious and permanent adverse effect from a vaccine and who meet other criteria.

Case reports and case series of illnesses following a vaccination may be published, but it is difficult to establish causality on this basis and, in fact, such reports may be misleading. The older literature is replete with case reports of illness following vaccination but in which a causal connection was never made. Certain reports have generated considerable controversies that have led to a decrease in vaccine use and to outbreaks of disease, emphasizing the necessity of performing controlled studies that can address the issue of causality. Randomized, double-blind, placebo-controlled trials of vaccines are required as part of the FDA approval process and are very reliable, but only common adverse events are detected.

The establishment of extensive databases provides a new resource for vaccine safety studies. The CDC is operating a Vaccine Safety Datalink (VSD) project, which links to the databases of eight health maintenance organizations with 6 million members. This database has been used for a number of population-based studies, including vaccine safety studies.[5] General information on vaccinations and reporting of adverse events is available from various internet sites (Table 48-3).

TABLE 48-2 ■ Neurologic Disorders Reported to the Vaccine Adverse Event Reporting System (VAERS)

Vaccine	Selected Neurologic Disorders Reported
MMR	Encephalitis, panencephalitis, aseptic meningitis, ADEM, cerebellar ataxia, parkinsonism, seizures, mental retardation, autism, GBS
Varicella	Headaches, stroke, aseptic meningitis, encephalitis, cerebellar ataxia, autism, developmental abnormalities, neuropathies
Zoster (Varzos)	Ataxia, brachial plexopathy
Influenza (quadrivalent)	GBS, MS, optic neuritis, acute axonal neuropathy, alien limb syndrome, antiganglioside antibody, autism, seizures
Influenza (H1N1)	GBS, seizures, autism, autoimmune neuropathy
Hepatitis A (HEPA)	Dyskinesia, ataxia, ageusia, antineuronal antibody
Hepatitis B (HEP)	MS, encephalitis, strokes, cerebellar ataxia, seizures, GBS, transverse myelitis, peripheral neuropathies, Bell palsy, myasthenia gravis, autism
Poliomyelitis (OPV)	Neuroparalytic disease, seizures, encephalitis
Rabies (Semple)	Neuroparalytic disease, GBS, stroke, ADEM, transverse myelitis, seizures, cranial and peripheral neuropathies
HPV (recombinant)	GBS, syncope, headaches, ALS, demyelinating neuropathy, dyskinesia
Japanese encephalitis	Encephalitis, seizures, ataxia
Yellow fever	Encephalitis, ADEM, acute hemorrhagic fever, seizures, optic neuritis, GBS, CIDP
DtaP	Seizures, encephalitis, meningitis, GBS, CIDP, ataxia, dyskinesia
Meningococcal (Menactra)	Encephalitis, meningitis, seizures, AHLE, stroke, demyelinating neuropathy, mononeuritis multiplex, antiganglioside antibody, antineuronal antibody
Pneumococcal (Prevnar)	Encephalitis, meningitis, TIA, stroke, demyelinating neuropathy, seizures, dyskinesia
Hib	Seizures, encephalitis, meningitis, stroke, neuropathy, autism, dyskinesia
Lyme	Aseptic meningitis, neuropathy, seizures

MMR, measles-mumps-rubella; ADEM, acute disseminated encephalomyelitis; GBS, Guillain–Barré syndrome; MS, multiple sclerosis; HPV, human papillomavirus; ALS, amyotrophic lateral sclerosis; CIDP, chronic inflammatory demyelinating polyneuropathy; DtaP, diphtheria-tetanus-pertussis; AHLE, acute hemorrhagic leukoencephalitis; TIA, transient ischemic attacks; Hib, Haemophilus influenzae type B.

Adjuvants and Preservatives

In order to attract the attention of the immune system and build an immune response, most vaccines require

TABLE 48-3 ■ Vaccine Web Sites

www.vaccine.org	General site of Allied Vaccine Group
www.cispimmunize.org	General information site
www.Vaers.hhs.gov	Vaccine Adverse Event Reporting System
www.cdc.gov/vaccines/ACIP/index.html	Advisory Committee on Immunization Practices
www.hrsa.gov/vaccinecompensation	National Vaccine Injury Compensation Program

the addition of an adjuvant. Aluminum salts such as aluminum hydroxide, aluminum phosphate, and aluminum potassium sulfate have been used safely in vaccines for more than 70 years. A recently developed adjuvant suspension used with the Shingrix vaccine is ASO1B. AS01B is made of up of monophosphoryl lipid A (MPL), an immune-boosting substance isolated from the surface of bacteria, and QS-21, a natural compound extracted from the Chilean soapbark tree. Adjuvants have to be carefully used and manufactured since they can lead to severe inflammation. The US Food and Drug Administration (FDA) does not currently approve the use of pure adjuvants outside of a vaccine.

Controversies around the safety of adjuvants have emerged in the last decades. The autoimmune/inflammatory syndrome induced by adjuvants (ASIA) is a term coined by Shoenfeld and co-workers. A careful review of over 300 cases of ASIA syndrome collected from an international registry revealed useful clinical information.[6] The mean age at disease onset was 37 years and the mean latency between adjuvant administration and development of symptoms was 16 months, ranging from 3 days to 5 years. The most frequent symptoms included arthralgias, myalgias, and chronic fatigue syndromes, but most patients had a concomitant autoimmune disorder, most commonly undifferentiated connective tissue disease (UCTD) and a positive antinuclear antibody test (ANA).

Perhaps the strongest evidence of the safety of aluminum in childhood vaccines came from a recent study that carefully assessed blood and hair aluminum levels, vaccination history, and cognitive, language, and motor development scores in children aged between 9 and 13 months. The authors found no correlation between infant blood or hair aluminum concentrations and vaccine history or between blood aluminum and overall developmental status.[7]

The mercury-containing preservative thimerosal has also been linked with neurologic complications, particularly with the risk of autism. Mercury is a naturally occurring element found in the Earth's crust, air, soil, and water. At high levels, it can be neurotoxic. Using standards for methylmercury, the FDA conducted an assessment of mercury content in vaccines and found that infants up to 6 months of age could receive quantities of mercury from vaccines that exceeded the recommended safety guidelines for methylmercury of the Environmental Protection Agency. Thimerosal, however, contains ethylmercury, not methylmercury. Ethylmercury is broken down and excreted much more rapidly than methylmercury and is therefore much less likely to accumulate in the body and cause harm.

Several efforts have been made to address concerns about the risk of autism and other developmental disabilities in children exposed to thimerosal. Reviews of the evidence by the Institute of Medicine concluded that evidence favored rejection of a causal association between thimerosal in vaccines and autism.[4] This conclusion was based on several factors. Large epidemiologic studies suggest that the incidence of autism in children who received thimerosal-containing vaccines is not different to those children that received thimerosal-free vaccines. Similarly, prenatal and early-life exposure to thimerosal from vaccines or immunoglobulins was not related to increased risk of autism.[8] In a US cohort study, standardized tests were administered to children between 7 and 10 years of age to assess the association between neuropsychologic performance and exposure to thimerosal from vaccines or immune globulins during the prenatal period, the neonatal period (0 to 28 days), and the first 7 months of life. The results did not support an association between early life exposure to mercury and deficits in neuropsychologic functioning at the age of 7 to 10 years.[9] As a precautionary measure, the United States has transitioned to a childhood vaccine schedule free of thimerosal. Currently, in the United States only multidose vial influenza vaccines contain preservative quantities (i.e., 25 μg per dose) of thimerosal, and thimerosal-free influenza vaccine preparations are widely available. Despite these changes, the incidence of autism continues to increase.

In conclusion, scientific evidence suggests that the presence of thimerosal in vaccines does not increase the risk of autism or other neurodevelopmental disorders.

Smallpox

Smallpox (or variola) is a highly contagious disease caused by a double-stranded DNA virus that is airborne.

Smallpox is mostly of historic significance at this time, but its potential as a weapon of biowarfare has drawn public health interest in smallpox vaccination issues. The illness begins abruptly with headache, fever, and back pain followed by a characteristic rash that begins on the face, followed by the arms and legs, and finally spreads to the torso. The rash begins with scattered macules and evolves into papules, vesicles, and finally pustules that then dry and crust over. The patient ceases to be contagious after the crusts fall off. There are two broad forms of the disease: the severe form, variola major, which had a mortality rate of about 30 percent, and a milder form, variola minor (alastrim), with a mortality rate of approximately 1 to 5 percent. There are several types of variola major, with the hemorrhagic smallpox form of the disease having a mortality of nearly 100 percent.

The original smallpox vaccination (variolation) involved the transfer of material from smallpox pustules or crusts into a scratch in the skin of the subject to be vaccinated. This method often resulted in a milder form of the disease, presumably because the preparation of the material from the smallpox lesions attenuated the smallpox virus contained therein. Variolation was the first example of an attenuated vaccine. However, the attenuation was often inadequate and some recipients developed full-blown smallpox as well as other diseases such as syphilis. Jennerian vaccination uses an animal poxvirus to induce cross-protective immunity against smallpox. The modern vaccine virus is not cowpox but vaccinia, a related virus; at what point cowpox was replaced by vaccinia or whether the original "cowpox" was some mixture of cowpox and vaccinia viruses is unknown.

Neurologic complications are uncommon. Recent series suggest that postvaccinal encephalitis can occur in 2 to 6 per million primary vaccinees, depending on age.[10] The risk in Europe is much higher, perhaps as high as 1 in 4,000, presumably because a different strain of vaccinia virus is used. There have been rare reports of isolation of vaccinia virus in the CSF in cases of encephalitis following vaccination. The overall death rate from all causes following smallpox vaccination is 0.5 to 5 per million vaccinees.

Measles, Mumps, and Rubella

Measles, mumps, and rubella were once common childhood illnesses in the developed world, but they became rare after the introduction of vaccines that prevent them. These vaccines are commonly given together in combination as the MMR vaccine. More recently, polyvalent vaccines have been introduced to minimize the number of injections to which small children are subjected. Formulations containing only some of these have been used in the past: measles (M) vaccine and measles plus rubella (MR).

MEASLES

Measles is a viral exanthem caused by an enveloped single-stranded RNA virus that is transmitted through the air and initially infects the respiratory epithelium, where it replicates. This replication gives rise to a primary viremia that implants virus in lymphoid tissues. A secondary viremia follows, and the virus is disseminated throughout the body. During measles a significant distortion of the immune system occurs, with paradoxic features. There is a nonspecific systemic immune activation, along with immunosuppression, causing susceptibility to bacterial and viral superinfections that are the main causes of morbidity and mortality and are enhanced by malnutrition, making measles a major cause of death in developing countries. The main complication of measles is pneumonia, due to bacterial superinfection in children and due to direct measles virus infection of the lungs in adults. Pneumonia occurs in roughly 10 percent of patients and causes more than 60 percent of the mortality resulting from the disease. Other complications include otitis media and laryngotracheobronchitis.

The main neurologic complication of measles, occurring in roughly 1 per 1,000 cases, is ADEM, in which multifocal inflammatory demyelination occurs within the central nervous system. ADEM may be due to molecular mimicry, since T cells from measles-associated ADEM patients proliferate upon exposure to myelin basic protein; cells from patients with uncomplicated measles do not. The mortality rate of ADEM is between 10 and 30 percent, and long-term sequelae are common and severe.

Measles virus was first isolated and propagated in tissue culture by Enders and Peebles in 1954, and efforts at making measles vaccine followed shortly thereafter. The first vaccines were made from the Edmonston B strain, which was obtained from the original Edmonston isolate (named after the individual from whom it was first obtained) by serial passage in primary kidney cells (24 passages), primary human amnion cells (28 passages), chicken embryos (6 passages), and then into chicken embryo cells. This vaccine was first introduced in 1963, but the high rate of fever and rash prompted its discontinuation. Other vaccine strains that were less reactogenic were then developed. One of these, the Moraten strain introduced in 1968, was derived from the Edmonston B strain by a further 40 passages in chicken embryo cells. Another strain, the Schwarz strain, was obtained from the Edmonston B strain by a further 85 passages in chicken embryo cells and was used from 1965 to 1976. The Moraten vaccine is the only one used in the United States today, although other vaccine strains are used elsewhere in the world. Before vaccination, 4 million cases of measles occurred annually in the United States, whereas there were only 309 cases in 1995 due to widespread vaccination.

Neurologic complications of measles vaccination have been reported but are uncommon. Case reports of encephalopathies do not, by themselves, provide evidence of causation. In order to better understand the risk of adverse events with measles vaccine, Weibel and co-workers analyzed data from claims of measles vaccine-induced encephalopathy submitted to the National Vaccine Injury Compensation Program.[11] In the years 1970 to 1993, 403 claims of postvaccination encephalopathy were reviewed; inclusion criteria included an acute encephalopathy 2 to 15 days after vaccination (M, MR, MMR) with permanent brain damage or death, with no other known cause that would explain the illness. Of these 403 purported cases, 48 met the criteria. The mean age of the cases was 17.5 months (range, 10 to 49 months).

Three main groups of complications were identified: ataxia, behavioral changes, and seizures. Fever preceded the encephalopathy in most, and one-quarter of the cases had a measles-like rash 1 to 2 weeks after vaccination. CSF was analyzed in most and was abnormal in 40 percent: pleocytosis was present in 70 percent, and protein concentration was elevated in more than one-third. No other viruses were found to be present. When the number of patients with encephalopathy was plotted against the day of onset, a typical epidemic curve was obtained with a peak at 8 to 9 days, suggesting a causal (rather than merely temporal) connection between the vaccination and the neurologic illness. Clinical and pathologic data do not point to any single neurologic disease entity. The risk of neurologic illness can be estimated from the fact that from 1970 to 1993, approximately 75 million children had measles vaccine by age 4 years, based on a 90 percent immunization rate and 83 million births. The limits of risk are, based on 48 claimants meeting criteria and on all 403 claimants, 0.64 to 5.37 cases per million vaccinees.

In a study of 1.8 million Finnish MMR vaccinees, actively surveyed from 1982 to 1996, adverse events included 77 that were neurologic and consisted mostly of febrile seizures with good recovery. One patient later developed Lennox–Gastaut syndrome. Four cases of encephalitis were reported, one of which was found to be due to herpes simplex virus; the others were uncharacterized. Some other neurologic complications were found to be due to other known causes (such as bacterial meningitis). Miscellaneous other neurologic disorders included cases of GBS (two patients, with eventual recovery), transient confusion, and transient ataxia. Interestingly, no cases of autism were found.[12]

MMR vaccine was proposed as a cause of autism, a complex and heterogeneous neurobehavioral syndrome. Much discussion has been stimulated by a report of 12 children who developed cognitive problems as well as inflammatory bowel disease a few days to a few months after receiving the MMR vaccine.[13] Questions were raised about the conduct of the study, with improper consent procedures, inconsistent use of data, irreproducibility of some laboratory findings, and failure to declare conflicts of interest. The interpretation of the paper as establishing a causal connection between MMR and autism was retracted by 10 of 12 authors who could be contacted. As further irregularities came to light, the paper was retracted in its entirety by the journal.[14]

The ages at which MMR vaccine is given are also the ages when autism manifests clinically; however, the beginnings of this behavioral disease occur much earlier in life. A report from the Institute of Medicine reviewed published and unpublished reports concerning the issue of MMR vaccine and concluded that there is no causal connection between the vaccine and autism.[4]

MUMPS

Mumps is an acute febrile illness caused by rubulavirus, a member of the paramyxovirus group. The clinical illness in children usually is self-limited, with fever, malaise, headache, and often an acute painful parotitis. The disease is complicated occasionally by meningitis and rarely by meningoencephalitis, which may lead to residual deficits. Sensorineural deafness is an uncommon sequela but can be a major cause of deafness in children during epidemics. In adults, mumps has a higher rate of systemic complications such as orchitis in men and oophoritis and mastitis in women, as well as pancreatitis and myocarditis. The main original vaccine virus strains were named the Jeryl Lynn and Urabe strains, after the hosts from which the original unattenuated viruses were isolated. Mumps vaccine was first licensed for use in 1967. The number of cases of mumps in the United States was over 150,000 in 1968 and decreased to less than 3,000 two decades later. The number of cases increased briefly after vaccination rates declined, but decreased again after mumps vaccination was required for school entry.

Aseptic viral meningitis is the main neurologic complication of mumps vaccination and is probably related to natural mumps frequently causing meningitis. The Urabe strain vaccine was discontinued in the United States after it was linked to aseptic meningitis in 1 case in 900 vaccinees in one Japanese series and 1 case in 200,000 vaccinees in another. For the Jeryl Lynn vaccine, the incidence is 1 case in 1.8 million vaccinees; by comparison, aseptic meningitis occurs in approximately 1 in 400 cases of natural mumps. This aseptic meningitis is self-limited and requires no specific therapy.

RUBELLA

Rubella is a self-limited viral infection in children, characterized by a fever and rash, caused by a single-stranded RNA virus. The virus causes most of its damage through prenatal infection. This congenital rubella syndrome is well described, and the triad of neurologic, eye, and cardiac defects is characteristic. The disease also includes a spectrum of uncommon disorders in all age groups including thrombocytopenic purpura, hepatitis, bone lesions, interstitial pneumonitis, diabetes mellitus, and thyroid problems.

The vaccine has very few complications in children, with rare mild rash and fever. In adults, the most common side effect of the vaccine is polyarthralgias. A few scattered reports of peripheral mononeuropathies and radiculopathy following rubella vaccination have been published,[15] but a review of these could not establish a causal relationship.[16]

Diphtheria, Pertussis, and Tetanus

DIPHTHERIA

Diphtheria is a disease caused by strains of *Corynebacterium diphtheriae*, which produce diphtheria toxin, a binary toxin consisting of two molecular components termed fragments A and B. Fragment B binds to the target cell and allows access of fragment A to the cytoplasm. Fragment A then inactivates elongation factor-2 (EF-2), inhibiting protein synthesis in the cell and leading to necrosis. Usually diphtheria infects the pharyngeal epithelium, where the superficial layers of the mucosa become necrotic and provide an excellent culture medium for the bacteria. These areas of tissue necrosis with exudation form the so-called diphtheritic "membranes." Systemic absorption of diphtheria toxin from the pharynx causes cardiac and neurologic effects. Patients with diphtheritic myocarditis may develop congestive heart failure; pathologic examination shows interstitial inflammation and hyaline degeneration of fibers. Diphtheritic "neuritis" includes several entities, including an isolated paralysis of the soft palate, ocular motor palsies, paralysis of the diaphragm, and a disorder resembling GBS. The pathogenesis of these various disorders is not understood.

In the 1920s, before diphtheria toxoid was introduced, there were approximately 100,000 cases in the United States annually. In the past few decades, no more than a handful of cases have occurred each year. When vaccine coverage decreases, large epidemics of the disease follow, as happened in Russia in the 1990s, when the public health infrastructure could no longer cover the population adequately. The mortality rate of the untreated disease is 30 to 50 percent. After the introduction of antitoxin therapy, the mortality rate declined to 10 to 20 percent; modern intensive care has reduced this rate further to 5 to 10 percent.

Vaccination against diphtheria was originally undertaken by injecting mixtures of toxin and antitoxin. In the early 1920s, it was found that treatment of diphtheria toxin with formalin resulted in a nontoxic immunogenic toxoid. This toxoid was incorporated with tetanus toxoid and inactivated whole-pertussis cells to make the diphtheria–pertussis–tetanus (DPT) vaccine that first became widely available in the mid-1940s.

There have been remarkably few neurologic complications from diphtheria toxoid, although they may be difficult to discern, as the toxoid is usually given in combination with pertussis and tetanus vaccines. Local injection-site reactions can be painful as they are intramuscular; infants may react with prolonged crying, irritability, drowsiness, loss of appetite, and vomiting. Limitation of abduction of the injected arm may occur regardless of age.

PERTUSSIS

Pertussis, or whooping cough, is caused by *Bordetella pertussis*, a commonly circulating bacterium that has multiple antigenic components. The disease begins with a seemingly minor upper respiratory infection, with minimal fever and an intermittent cough, that then becomes severe and progresses to paroxysms in which coughing becomes very vigorous, interfering with breathing and increasing intracranial pressure by continual coughing. This paroxysmal stage lasts between 2 and 6 weeks before resolving.

The disease was commonly lethal in the past. At the beginning of the 1900s, approximately 5 of every 1,000 liveborn infants died of pertussis before 5 years of age. Today, there are fewer than 10 deaths per year in the United States. When vaccine coverage declines, the disease re-emerges because pertussis vaccine protects only against bacterial toxins but does not necessarily eliminate the pathogen from the population (unlike smallpox, for example). The pathogenesis of the disease is not completely known, but is probably due to a toxic effect on respiratory epithelium with denudation of respiratory passages.

An important complication of pertussis is pertussis encephalopathy, a vaguely described syndrome of encephalopathy and seizures. In the years 1997 to 2000, pertussis encephalopathy and seizures occurred in 0.1 and 0.8 percent of cases, respectively. There appear to be two clinical forms, one with an abrupt onset of seizures and coma and the other with the gradual onset of somnolence progressing to coma. The prognosis appears to be rather poor, with death, permanent cognitive deficits, and recovery each occurring in one-third of cases. The pathologic changes are characterized by vascular congestion and brain petechiae. The pathogenesis probably involves the effects of anoxia and increased venous pressure in the brain caused by the severe cough. Interestingly, intravenous injection of toxin does not appear to cause neurologic complications.

Pertussis vaccine has dramatically decreased the burden of disease in vaccinated populations; it declined from about 200,000 cases in the United States in the mid-1930s to a nadir of 1,010 cases in 1976, with a subsequent increase to about 8,000 cases occurring in 2000 for unclear reasons. The original vaccine consisted of inactivated whole bacterial cells. Whole-cell vaccine is "reactogenic," causing painful local injection-site reactions and fever. The latter can lead to febrile seizures in children, who are especially susceptible. This reaction triggered reports of severe neurologic illnesses following pertussis vaccination which likely were related in many cases to the fever alone.

To ascertain the risk of neurologic illness attributable to pertussis vaccine, an active survey of encephalopathic illnesses was performed in all British children from July 1976 to June 1979 in the National Childhood Encephalopathy Study. A comparison was made of rates of vaccination in those with or without encephalopathy. A small excess of patients with encephalopathy was found following vaccination. All vaccines with a pertussis component, for example, pure pertussis vaccination, DPT vaccination, and diphtheria–pertussis (DT) vaccination, were counted as pertussis vaccination. The study's methodology has been criticized, and it is likely that other concurrent diseases in part explained the neurologic problems. In particular, some severe epileptic encephalopathies (Dravet syndrome), due to mutations in sodium channels, manifest themselves at the same age that pertussis vaccine is given. Furthermore, there were problems with choice of controls, blinding of investigators, misclassification of cases, and uncertainties regarding the onset of disease. These questions about the conduct of the study have been elaborated in published critiques and these risk estimates are no longer used by the British legal system as a basis for estimating liability.[16]

A new acellular vaccine consisting only of a subset of antigenic components of the bacterial cell was introduced in 1996 and appears to be much less reactogenic.

TETANUS

Tetanus is a neurologic disease caused by *Clostridium tetani*, which is present ubiquitously in soil. The organism has two toxins carried on a plasmid: tetanospasmin, the neurotoxic component, and tetanolysin, which is a hemolysin. Tetanospasmin is elaborated locally and transported to the CNS in the blood and via local axonal transport. It interferes with release of the presynaptic inhibitory neurotransmitters glycine and γ-aminobutyric acid (GABA), causing inappropriate disinhibition of spinal cord reflex arcs, with resultant greatly increased tone in the muscles and intermittent painful spasms. Respiratory compromise may lead to death. The toxin is very potent, a lethal dose being only 2.5 ng/kg. The case fatality ratio of the untreated disease is 25 to 70 percent overall and 100 percent at the extremes of age; with intensive care, the mortality rate decreases to 10 to 20 percent.

Tetanus toxoid consists of formalin-treated tetanospasmin, which induces an immune response that provides good protection lasting around 10 years. Adverse events are rare and are mostly anecdotal. Brachial plexopathy occurs in 1:100,000 vaccinees within 1 month of vaccination, and there may be a slightly increased risk of GBS (0.4 per million doses). One person had an illness resembling GBS on each of three vaccinations with tetanus toxoid.

Influenza

Influenza is an acute, febrile, debilitating viral infection of the upper respiratory tract that causes significant work and school absences each year. It can be complicated by pneumonia and, rarely, by ADEM. In children, the complications of influenza or its treatment include encephalopathies such as Reye syndrome as well as a toxic encephalopathy of unclear nature, possibly related to cytokine production in the course of disease. The virus was first isolated in 1933. In 1935, neutralizing antibodies were detected in subjects given subcutaneous injections of influenza virus. The first trial of an influenza vaccine demonstrated some degree of protection in 1936. The virus at the time was grown in a suspension of mouse lung and then injected into children. Further studies of influenza vaccination using inactivated virus were carried out by the military in the early 1940s with clear benefit, leading to the licensing of influenza vaccines in the United States in 1945. In 1947, a dramatic failure of the vaccine during an influenza epidemic led to the discovery that the vaccine produced immunity to the vaccine virus but not to the epidemic strain as a result of antigenic change in influenza virus. Such change can be of two types: (1) antigenic drift, in which the accumulation of mutations in the genes coding for the surface antigens of the virus renders it sufficiently different from the previous strains so that it can cause disease despite exposure to the previous virus, and (2) antigenic shift, in which there is reassortment of genes coding for the surface proteins from viruses circulating between birds and pigs. This experience led to the establishment of worldwide sentinel centers by the World Health Organization, which monitor for new strains of influenza virus every year so that the new strains can be incorporated into the updated vaccine. The recent circulation of the H5N1 strain in Southeast Asia is of great concern because of the highly lethal nature of the disease and its potential for human-to-human transmission.

Current vaccines are of two types. An inactivated vaccine uses two strains of influenza A and one influenza B virus, all grown in embryonated chicken eggs and inactivated with β-propiolactone. A cold-adapted attenuated vaccine, containing two influenza A and one influenza B attenuated strains, has been introduced and is given as a nasal spray.

In 1975, a fatal case of swine flu in a military recruit prompted the institution of a national swine flu vaccination program because of the fear that the outbreak would resemble the 1918 influenza epidemic that caused such widespread mortality. The vaccine was produced, and 45 million doses were administered by mid-December 1976. In late November and early December 1976, cases of GBS were reported to local health departments and prompted an investigation of the relationship to the flu vaccine. The results of an active surveillance of all such cases reported during the period of vaccination, prompted by reports of a possible causal connection and requested by a court in which a lawsuit had been filed, uncovered 1,300 possible cases, of which 944 could be evaluated.[17] There were 504 cases in vaccinees and 440 cases in nonvaccinees. Although the data were insufficient to diagnose GBS definitively, the cases could be classified by the extent of involvement into "extensive" and "limited" paresis. When the distribution of cases was plotted as a function of time since vaccination, the "extensive" cases followed a typical log-normal epidemic curve, whereas cases of limited paresis did not, implying a causal relationship between vaccination and GBS in a small number of cases. The effect of the vaccine lasted 6 to 8 weeks, and the actual risk of GBS attributable to vaccine was 4.8 to 5.9 per million vaccinees. Interestingly, no such increased risk was found in England and the Netherlands, as well as in 1.7 million US military personnel who received a double dose.[17] Furthermore, there was no increased risk of GBS following influenza vaccination in other subsequent seasons. The threat of severe influenza pandemics remains, and antigenic shifts are likely to challenge us with high-morbidity pandemics.

In the late 1990s, an H5N1 outbreak among chickens in Hong Kong led to a number of human deaths, although the virus was not easily transmissible to humans. Since then, the virus has appeared in many other countries but has not led to many human infections, which is fortunate since the case fatality rate is high in both humans and birds.

Despite a theoretical concern for the safety of influenza vaccines in patients with a history of multiple sclerosis and central demyelination, it appears to be quite safe. There was no increase in the onset or relapses of multiple sclerosis in a retrospective study following swine flu vaccine. There were also no increases in relapse rate in a double-blind trial involving 66 patients with multiple sclerosis.[18] Nonswine influenza vaccines are safe to use in multiple sclerosis, and a case-control study of influenza vaccine performed by the Vaccine Safety Datalink Study Group demonstrated no association with either multiple sclerosis or optic neuritis.[18] The same study also showed no association between vaccination against hepatitis B, tetanus, measles, or rubella and either multiple sclerosis or optic neuritis. The Immunization Safety Review Committee of the Institute of Medicine concluded that there was sufficient evidence to reject any causal relationship between such relapses and influenza vaccination.[4]

Hepatitis B

Hepatitis B is caused by a hepadnavirus, a partially double-stranded DNA virus, which is endemic worldwide, especially in sub-Saharan Africa and Southeast Asia. The virus is present in blood and semen and can thus be transmitted sexually and through inadequately processed blood products. The disease is usually self-limited in adults, with a clinical spectrum of asymptomatic infection to severe disease, followed by resolution and clearance of virus. However, in infants and children (80 to 90% of those infected before 1 year) as well as in some adults (approximately 5% of those infected), the acute infection is often asymptomatic but evolves into a chronic active hepatitis, with progression to cirrhosis and possibly hepatocellular cancer. In highly endemic areas such as sub-Saharan Africa and Southeast Asia, this is one of the most common cancers, leading to significant mortality.

In 1991, two cases of central demyelination were reported after receipt of the recombinant hepatitis B vaccine, one being in a patient with pre-existing multiple sclerosis. A report of eight patients with disseminated central demyelination with persistent activity on imaging studies caused much controversy in France.[19] After other cases were subsequently reported, calculations of the expected number of new cases of multiple sclerosis (1 to 3 per 100,000 annually) showed that the disease incidence in the vaccinees (0.65 per 100,000 annually) was actually less than would have been expected.[19] A population-based retrospective cohort study of 134,698 persons compared the rate of CNS demyelination in hepatitis B vaccinees with that in nonvaccinees and found no difference. In a case-control study from British Columbia, the rates of development of multiple sclerosis in adolescents vaccinated against hepatitis B in the years 1992 to 1998 (after universal hepatitis B vaccination became standard) were compared with those not vaccinated in the years 1986 to 1992 (before the vaccine was available); no statistically significant difference was found between the two groups.[19] A multicenter hospital-based study in France also found no evidence of an association between central demyelination and receipt of hepatitis B vaccine. There is therefore no evidence of causality between hepatitis B vaccination and multiple sclerosis. Other studies have found no evidence that hepatitis B vaccine triggers relapses in patients with established multiple sclerosis.[19]

Poliomyelitis

Poliomyelitis, caused by poliovirus type 1, 2, or 3, usually is asymptomatic or consists of a mild febrile illness in early childhood. In older children, adolescents, or adults, the febrile illness may be accompanied by damage to the anterior horn cells in the spinal cord. The disease is spread by fecal–oral contact and caused considerable morbidity before vaccination became widely available.

Early attempts at vaccination in the 1930s were disastrous—inadequate attenuation of the virulent virus led to polio in recipients (there was no test for attenuation of viruses), different serotypes were unknown and therefore not protected against, and there were no safety precautions against injecting neurally derived material. In the Cutter incident, which was associated with the Salk inactivated vaccine, 260 vaccinees and contacts contracted polio. These cases were thought to be related to the vaccine because they occurred in just a few western states, all were injected by vaccine supplied by a single manufacturer (Cutter Laboratories), the injected extremities were disproportionately affected, and the cases were traced to lots that were found to be inadequately attenuated.

The Sabin oral vaccine consists of attenuated virus that replicates in the gut and induces immunity in both the vaccinee and contacts (because the vaccinee sheds vaccine virus). Rarely, however, the virus reverts to a virulent form and may cause vaccine-associated paralytic poliomyelitis in 1 per 1 million doses in vaccinees or their contacts. Because the only polio seen in North America was vaccine associated, the Sabin vaccine was withdrawn from use in 1994. It is still in use in other parts of the world and has occasionally caused small epidemics of paralytic disease, with a recently reported outbreak occurring in China in 2004.

EMERGING VIRUSES

The global burden of viral disease is increasing. Arboviruses (arthropod-borne viruses) play an important role due to climate factors that encourage the growth of arthropod populations, greater access to various means of transportation, and exploration of previously isolated areas. Some of the most important of these viruses result in dengue fever, Japanese encephalitis, tick-borne encephalitis, and West Nile fever. These viruses have achieved prominence because of an increasing number of infections and disease with an increasing geographic spread.

Dengue, for instance, has not only reached a very high incidence rate but has become more severe, resulting in dengue hemorrhagic fever and dengue shock syndrome. Some dengue encephalitis cases have also been reported. Dengue hemorrhagic fever and dengue shock syndrome occur in areas where more than one (of four) serotypes cocirculate. Infection with one serotype confers protection against that serotype but enhances the effects of other serotypes. The implications for vaccine design are obvious. A phase 2 trial of an attenuated tetravalent vaccine in 3,673 participants, given at 0, 6, and 12 months, demonstrated that a safe vaccine against dengue is possible.

Another important threat to public health is enterovirus 71, which can cause an undifferentiated febrile illness, hand-foot-and-mouth disease, and has been associated with a brainstem encephalitis in children with a high case fatality rate (see Chapter 42). Already vaccines against enterovirus 71 are in phase 3 trials after demonstration of efficacy and safety in a 1,200-participant phase 2 trial.

THERAPEUTIC VACCINATION

Other potential uses for vaccines that are evolving include therapeutic vaccines, meant to modify or abolish an already established disease process, rather than to prevent the disease from beginning. Such a strategy has been attempted in the treatment of Alzheimer disease in which a β-amyloid fragment was used to immunize patients against disease-causing β-amyloid. Unfortunately, despite success in rodent models, several patients developed an immune-mediated encephalitis. A similar strategy may be useful in prion disease, if an appropriate antigen can be identified. A vaccine that could cause an immune deviation from a Th2 to a Th1 response may be useful in chronic intracellular infections that stimulate a humoral immune response (Th2) rather than the more effective cell-mediated immunity (Th1). Cancer vaccines have also been investigated and at least two are in clinical trials for prostate adenocarcinoma and melanoma.

CONCLUDING COMMENTS

Prevention of infectious diseases through active immunization is perhaps one of the greatest public health achievements to date. As a result of the development of new vaccines coupled with successful immunization programs, the epidemiology of various infectious diseases has been markedly altered. As an example, prior to the introduction of the conjugate vaccine, the incidence of Hib meningitis was between 10,000 and 20,000 cases per year in the United States and Canada, with a 3 percent mortality rate. Nowadays the incidence of invasive Hib disease is 0.08 cases per 100,000 in children younger than 5 years of age.

Like any other therapies, vaccination carries certain risks. It is biologically plausible that neurologic syndromes following vaccinations are caused by the active ingredient in the vaccine or the adjuvants. There is a theoretical basis by which vaccines could cause neurologic complications, often through immune-mediated mechanisms. In most cases, however, the lack of proven putative association between vaccinations and neurologic injury make it challenging to determine a coincidental or causative relationship (Table 48-4).

TABLE 48-4 ■ Potential Neurologic Complications of Vaccinations that Reached Public Concern

Vaccine and Potential Complication	Evidence
MMR vaccine and autism	Large epidemiologic studies have not found an increased risk of autism associated with MMR vaccine
Thimerosal and autism	Large epidemiologic studies have not found an increased risk of autism or other neurodevelopmental disabilities associated with thimerosal-containing vaccines.
Influenza vaccine and GBS	Increased risk was found with the 1976 swine influenza vaccine. Findings have been mixed with subsequent seasonal influenza vaccines
Influenza vaccine and MS	Epidemiologic studies have not supported the hypothesis that vaccines cause MS
HPV vaccine and autoimmune disorders	Several large population-based studies have not found increased risks of autoimmune or neurologic diseases
Aluminum and autoimmune disorders	No correlation found between infant blood or hair aluminum concentrations and vaccine history

MMR, measles-mumps-rubella; GBS, Guillain–Barré syndrome; MS, multiple sclerosis; HPV, human papillomavirus.

Concerns about vaccine safety can lead to decreased acceptance of vaccines and resurgence of vaccine-preventable diseases. This is often due to the fact that the public often underestimate the risk of naturally acquired infectious diseases and overestimate the risks of vaccines. The CDC recently released data on the greatest measles outbreak in the United States with over 1,200 patients reported in 2019. The majority of cases were among people who were not vaccinated against measles.[20] Given these issues, it is imperative to continue our efforts to increase surveillance of potential adverse events associated with vaccinations, continue to educate our patients on the potential risks of resurgence of certain infections, and continue efforts to deepen our understanding of biologic plausibility between vaccinations and neurologic complications.

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CHAPTER

49

Sarcoidosis of the Nervous System

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SARCOIDOSIS

PATHOPHYSIOLOGY

EPIDEMIOLOGY

NEUROLOGIC MANIFESTATIONS

- Cranial Neuropathy
- Meningeal Disease
- Hydrocephalus
- Parenchymal Disease
  - *Endocrine Disorders*
  - *Mass Lesions*
  - *Encephalopathy-Vasculopathy and Stroke*
  - *Seizures*
  - *Myelopathy*
- Peripheral Neuropathy
- Myopathy

DIFFERENTIAL DIAGNOSIS

- Presence of Systemic Sarcoidosis
- Diagnosis of Neurosarcoidosis
- Isolated Neurosarcoidosis

TREATMENT

- Cranial Neuropathy
  - *Peripheral Facial Palsy*
  - *Other Cranial Nerve Palsies*
- Aseptic Meningitis
- Hydrocephalus
- Parenchymal Disease
- Peripheral Neuropathy and Myopathy

IMMUNOSUPPRESSIVE AND IMMUNOMODULATORY TREATMENTS

GENERAL SUPPORTIVE CARE

PROGNOSIS

Sarcoidosis was first described in 1877 by Sir Jonathan Hutchinson as a disease of the skin. At the turn of the century, Caesar Boeck termed the disease *multiple benign sarkoid*, because of its histologic similarity to sarcoma, and from this is derived the modern term *sarcoidosis*. Boeck also demonstrated the unifying pathologic feature of sarcoidosis as epithelioid cell granulomas that could involve different organs. Sarcoidosis is today recognized as a multisystem granulomatous disorder of unknown etiology. Typical presentations include bilateral hilar adenopathy, pulmonary infiltration, and skin and eye lesions.

Neurologic involvement in sarcoidosis was first reported in the early 1900s by Heerfordt, who described patients with cranial nerve palsies. Varied neurologic manifestations of sarcoidosis are now recognized to occur in approximately 5 to 10 percent of patients. Neurosarcoidosis manifests in diverse ways, including with cranial neuropathies, aseptic meningitis, mass lesions, encephalopathy-vasculopathy, seizures, hypothalamic–pituitary disorders, hydrocephalus, myelopathy, peripheral neuropathy, and myopathy. Because its neurologic manifestations are so diverse, its etiology is unknown, and confirmative laboratory tests are lacking, neurosarcoidosis frequently poses a diagnostic challenge. The diagnosis of neurosarcoidosis is usually based on the identification of a characteristic neurologic presentation in an individual with systemic sarcoidosis; however, neurologic manifestations are the presenting feature in approximately 50 to 75 percent of patients with neurosarcoidosis. Optimal management of patients with neurosarcoidosis requires an understanding of the broad clinical spectrum of the disorder, the best methods of confirming the diagnosis, and the full range of treatment options.

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SARCOIDOSIS

The 1976 internationally accepted definition of sarcoidosis remains of value today: "sarcoidosis is a multisystem granulomatous disorder of unknown etiology, most commonly affecting young adults and presenting most frequently with bilateral hilar adenopathy, pulmonary infiltration, skin or eye lesions. The diagnosis is established most securely when clinical and radiographic findings are supported by histologic evidence of widespread noncaseating epithelioid-cell granulomas in more than one organ." Sarcoidosis usually presents between the ages of 30 and 55 years but can occur in children as well as in older populations. The highest incidence and prevalence of sarcoidosis have been reported in Nordic European populations and African-Americans.[1] The clinical manifestations of sarcoidosis are similar across populations. Intrathoracic structures are most commonly affected, followed by lymph nodes, skin, and ocular disease. Approximate frequencies of organ manifestations are indicated in Table 49-1, although they vary across reported cohorts. Although a diagnosis of sarcoidosis is most secure when it is based on histologic confirmation, in around 30 percent of patients the diagnosis is based solely on clinical and radiologic findings—frequently in patients presenting with classic Löfgren syndrome (an acute form of sarcoidosis characterized by bilateral hilar lymphadenopathy, erythema nodosum, and polyarthralgia).

TABLE 49-1 ■ Frequency of Organ Involvement in Sarcoidosis

Manifestation	Approximate Frequency (%)
Intrathoracic	89–99
Hilar nodes	50–85
Lung parenchyma	45–55
Upper respiratory tract	5
Skin	16–35
Erythema nodosum	10–14
Ocular	5–60
Parotid gland	4–6
Liver or spleen	5–50*
Peripheral lymphadenopathy	12–60
Bone	3–13
Cardiac	5–40*
Hypercalcemia	10–20
Renal calculi	10–15
Neurologic	5–15
Hematologic, endocrinologic, and luminal gastrointestinal	Rare

*Involvement of these organs is frequently not clinically apparent and is only detected on imaging, biopsy, or autopsy.

Involvement of any organ by sarcoidosis is possible and may occur with or without symptoms. It is estimated that 20 to 40 percent of patients are asymptomatic at presentation, their disease being discovered by routine chest radiography. In fewer than 10 percent of patients, the onset of symptoms is neither systemic nor pulmonary. Neurologic presentations of sarcoidosis fall in this category.

Many laboratory abnormalities have been described in sarcoidosis, but no specific or highly sensitive diagnostic test is available. Active sarcoidosis may cause an elevation in serum angiotensin-converting enzyme (ACE), which can then serve as a marker of systemic disease activity, but serum ACE is nonspecific, and often elevated in patients with other conditions such as liver disease, diabetes mellitus, hyperthyroidism, systemic infection, malignancy, and Gaucher disease.

Most patients with systemic sarcoidosis have a good prognosis. For approximately two-thirds, the disease resolves spontaneously without major difficulties. This benign course is most common in Löfgren syndrome or in asymptomatic patients with only hilar adenopathy on chest radiographs; they have a high chance of spontaneous remission. However, for one-third of patients, symptoms persist or the disease progressively worsens. Pulmonary dysfunction is the major issue for most patients with a persistent or progressive clinical course. Mortality in systemic sarcoidosis is reported as below 5 percent. Deaths are most often due to respiratory failure, although neurologic and cardiac involvement can also be fatal.

The basis of treatment for all forms of sarcoidosis is immunotherapy, most frequently with corticosteroids. However, debate continues as to the precise indications for treatment, because many patients are asymptomatic at the time of presentation and the rate of spontaneous resolution is high. In addition, the clinical presentation and course are so varied that treatment studies—particularly large, well-controlled studies—are lacking. Corticosteroid treatment seems most clearly indicated for patients with significant functional impairment in any organ system, particularly with major pulmonary, cardiac, ocular, or central nervous system (CNS) involvement. Alternative immunosuppressive treatment options are discussed in detail later.

PATHOPHYSIOLOGY

Although the precise etiology of sarcoidosis remains unknown, major strides have been made in understanding its pathogenesis. There is strong evidence that sarcoidosis is caused by heightened immune processes at sites of disease activity. Environment and heredity are both likely to play a role in the etiology of the disorder, with potential complex interactions between environmental triggers and genetic, immunologic, and epigenetic factors.

Current understanding of the immunopathology of sarcoidosis derives largely from studies of pulmonary sarcoidosis. The initial lesion in pulmonary sarcoidosis is an alveolitis, an inflammation of the alveolar structures of the lung (Fig. 49-1). Undoubtedly, processes similar to those in the lung underlie the pathogenesis of other forms of sarcoidosis, including neurosarcoidosis (Fig. 49-2).

The central pathologic hallmark of sarcoidosis, the granuloma, consists of macrophages, macrophage-derived epithelioid cells, and multinucleated giant cells that secrete cytokines (Fig. 49-3). Surrounding this central core are $CD4^+$ and $CD8^+$ T lymphocytes, B lymphocytes, plasma cells, and fibroblasts.

Unfortunately, the inciting antigen or antigens remain unknown. Among the suspected causes have been infectious agents and environmental exposures such as pine pollen and silica. Of the various possible infectious inciting antigens, mycobacterial infections and *Propionibacterium* species have received the most attention. More recently, genetic research has linked several genes (particularly in the HLA region) to disease risk or phenotype.

It is thought that in reaction to an antigen, monocytes and macrophages form granulomas, and ultimately irreversible obliterative fibrosis can develop. Small foci of ischemic necrosis occur, probably as a consequence of in situ thrombosis due to perivascular inflammation. Importantly, granulomas are not specific for sarcoidosis, and nearly identical lesions occur in a variety of other conditions.

The pathology of neurosarcoidosis is characterized by noncaseating granulomas and the accompanying diffuse mononuclear cell infiltrates that can be found in any part of the neuraxis, including peripheral nerve or muscle. The most common site of inflammation is the meninges, especially in the basal region of the brain (Figs. 49-4 and 49-5). Sarcoid granulomas may be widely distributed or concentrated in one or more areas to form a mass lesion. Although sarcoidosis is not usually considered to be a primary vasculitis, arteriolar and venous infiltration can occur and may lead to infarction.[2] The granulomatous inflammation found pathologically may correlate directly with clinical deficits or may be subclinical.

Inflammation affecting primarily the leptomeninges may spread along Virchow–Robin perivascular spaces to invade the brain or spinal cord, or it may remain more localized, involving the cranial nerves. Inflammation can also extend to the cerebrospinal fluid

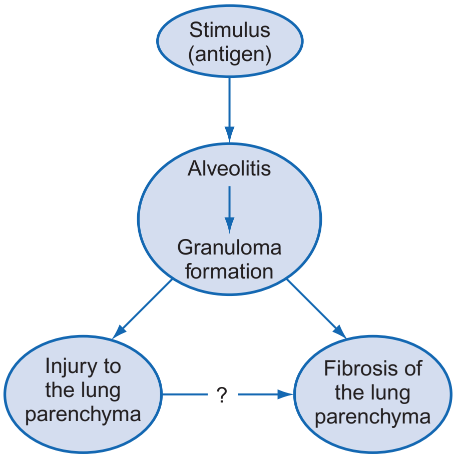
Stimulus
(antigen)
Alveolitis
Granuloma
formation
Injury to
the lung
parenchyma
?
Fibrosis of
the lung
parenchyma

FIGURE 49-1 ▪ Postulated mechanisms of pulmonary damage in sarcoidosis.

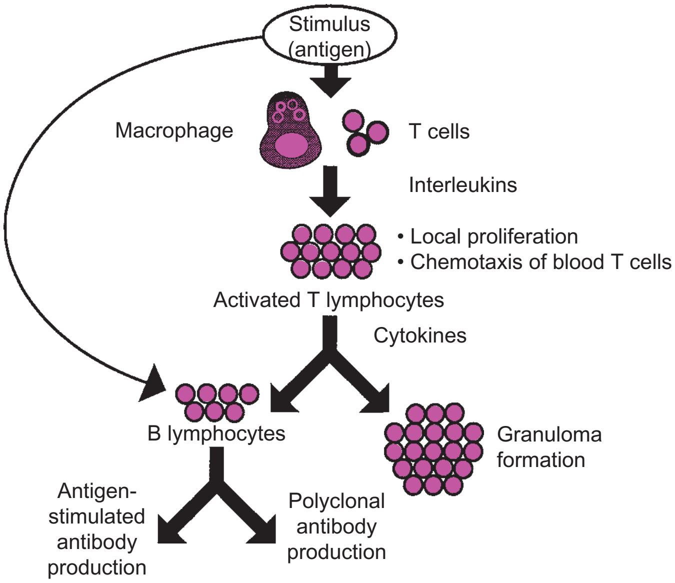
Stimulus
(antigen)
Macrophage
T cells
Interleukins
• Local proliferation
• Chemotaxis of blood T cells
Activated T lymphocytes
Cytokines
B lymphocytes
Granuloma
formation
Antigen-
stimulated
antibody
production
Polyclonal
antibody
production

FIGURE 49-2 ▪ Immunologic mechanisms active in the pathogenesis of granulomatous inflammation in neurosarcoidosis.

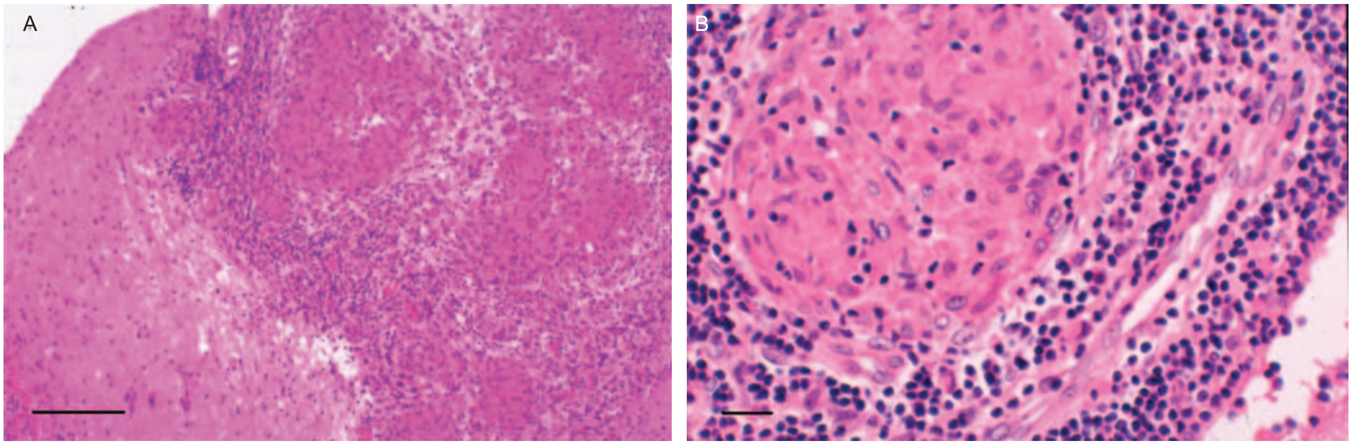

FIGURE 49-3 ■ Brain-biopsy section stained with hematoxylin and eosin. *A*, Low-magnification photomicrograph showing dense granulomatous inflammation involving the leptomeninges, with underlying gliotic cerebral cortex in a patient with neurosarcoidosis (scale bar, 50 μm). *B*, High-magnification photomicrograph showing Virchow–Robin space involvement by a collection of epithelioid histiocytes (granulomatous inflammation) and lymphocytes in a patient with neurosarcoidosis (scale bar, 20 μm).

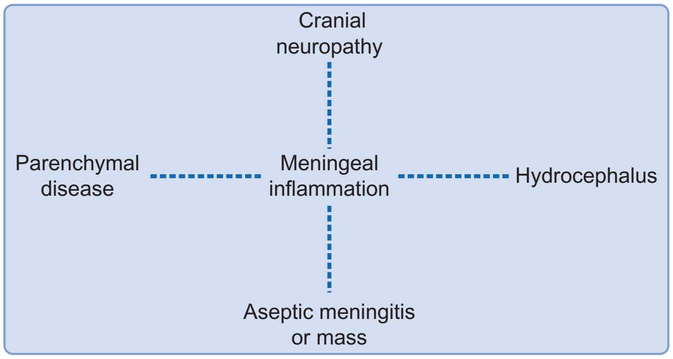

FIGURE 49-4 ■ Central nervous system sarcoidosis: clinicopathologic relationships.

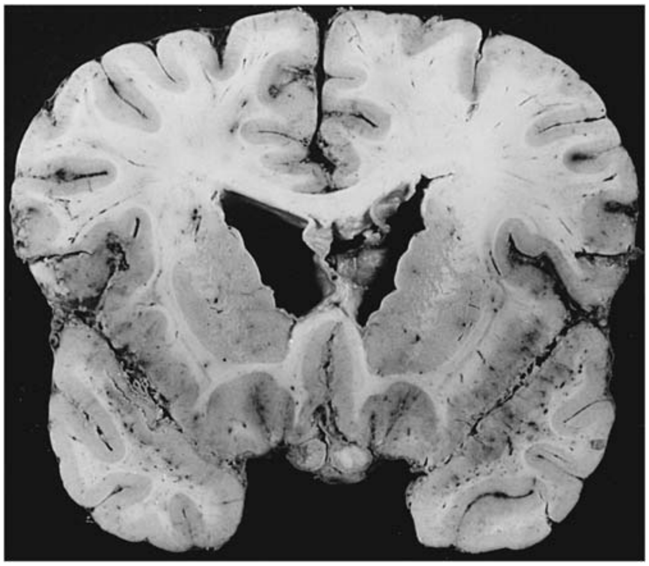

FIGURE 49-5 ■ Coronal midfrontal pathologic section of the brain of a patient with neurosarcoidosis, showing thickening and inflammatory changes of the basal meninges and optic chiasmal region.

(CSF)-containing spaces, leading to hydrocephalus. Brain or spinal cord disease may appear as discrete granulomatous mass lesions or as diffuse parenchymal disease with or without vasculopathy. The hypothalamic region is the most common site of parenchymal disease.

Granulomas can also be found in the epineurium and perineurium of peripheral nerves. The endoneurium may contain a mononuclear cell infiltrate. Perivascular and vascular inflammation may be seen in the epineurial and perineurial vessels. Nerve fibers of all sizes can be affected; a predominantly axonal neuropathy is usual, with only minor segmental demyelination.

Muscle pathology may also occur in sarcoidosis. Muscle biopsy of symptomatic patients reveals typical noncaseating granulomas. More diffuse inflammation can occur, with muscle fiber degeneration along with regeneration and fibrosis. Asymptomatic noncaseating granulomas are found in as many as one-half of all patients with systemic sarcoidosis undergoing muscle biopsy.

EPIDEMIOLOGY

The prevalence of sarcoidosis is estimated to be on the order of 60 per 100,000 population, with an annual incidence of approximately 11 per 100,000 population, although this incidence likely varies regionally and in population subgroups.[1] The exact prevalence and incidence are difficult to validate because of diagnostic challenges. Sarcoidosis can occur at any age, with peak onset between age 30 and 55.[1]

Population differences for sarcoidosis have been well-described. In the United States, incidence is increased in African-Americans compared with Caucasians. The disease also seems to be more severe in African-Americans.[1] Certain areas of the world, such as in Sweden and other Nordic European countries, have a higher incidence of sarcoidosis, whereas it is quite rare in China and Southeast Asia. First-degree relatives of patients with sarcoidosis appear to have a higher risk of the disease, as do monozygotic twins compared to dizygotic twins.[3] Genetic studies using a range of techniques including genome-wide association studies, HLA typing, and fine-mapping have identified multiple genetic variants associated with sarcoidosis risk, potentially accounting for 33 percent of disease heritability.[3] In addition, genetic variants such as HLA subtypes may be associated with disease phenotype.[3] Notably, a significant association with a variant in the *ZNF592* gene has been identified in patients with neurosarcoidosis.[4]

NEUROLOGIC MANIFESTATIONS

Neurologic symptoms are the presenting feature of sarcoidosis in around 50 to 75 percent of individuals with neurosarcoidosis, and in other patients neurologic manifestations often occur a short time after systemic diagnosis (usually less than 2 years).[5] Only rarely do patients with neurosarcoidosis have no evidence of even asymptomatic disease in other organ systems such as the lungs, a condition termed "isolated neurosarcoidosis." The approximate frequency of the various neurologic complications is presented in Table 49-2, although numbers vary across reported cohorts.[5,6] One-third to one-half of patients with neurosarcoidosis will eventually develop more than one neurologic manifestation of their disease.

Cranial Neuropathy

The most frequent neurologic complication of sarcoidosis is cranial neuropathy, occurring in over half of patients with neurosarcoidosis.[5] Any cranial nerve can be involved, but the facial nerve is most commonly affected. Around one-third to one-half of patients will have involvement of multiple cranial nerves.[5]

TABLE 49-2 ■ Complications of Neurosarcoidosis

Clinical Manifestation	Approximate Frequency (%)
Cranial neuropathy	50
Facial palsy	25
Aseptic meningitis	15
Hydrocephalus	10
Parenchymal disease	
Endocrinopathy	10–15
Mass lesion(s)	5–10
Encephalopathy-vasculopathy	5–10
Seizures	10
Myelopathy	15
Radiculopathy/neuropathy	15
Myopathy	10

Olfactory nerve dysfunction may occur secondary to meningeal sarcoidosis involving the subfrontal region. However, anosmia or hyposmia may also result from local nasosinus granulomatous invasion. *Optic nerve* involvement is much less frequent than other ocular manifestations of sarcoidosis such as uveitis, but is reported in around 15 to 20 percent of cases of neurosarcoidosis.[5] Optic neuropathy can present with visual loss that is acute, subacute, or chronic, can be painful or painless, and may be bilateral. The visual loss may be due to bulbar or retrobulbar invasion of the optic nerve by granulomas or extrinsic compression of the optic nerve by a granulomatous mass.[7] Intraocular inflammation such as anterior uveitis may co-occur. Optic disc edema may be secondary to papilledema from sarcoidosis-induced increased intracranial pressure (typically with meningitis) or result from direct local invasion by sarcoid. A chiasmal syndrome also has been reported.

Disorders of ocular motility may follow involvement of the *oculomotor*, *trochlear*, or *abducens nerves*. Typically, these nerves are damaged in their extra-axial course in the subarachnoid space as they traverse the meninges or the cavernous sinus (where mass-like inflammatory lesions can occur).[7] However, they may also be involved in local orbital disease, and rarely the brainstem nuclei themselves and eye movement pathways can be affected. Occasionally, pupillary dysfunction is present. Uncommonly, disordered ocular motility is due to sarcoidosis involving the extraocular muscles directly.

Trigeminal nerve disease may present as facial numbness or, rarely, trigeminal neuralgia. Headache may also represent trigeminal nerve dysfunction intracranially. Involvement of the muscles of mastication is unusual.

Of the cranial nerve syndromes, peripheral *facial nerve* palsy is the most common, and it is also the single most frequent neurologic manifestation of sarcoidosis. It develops in around one-quarter of all patients with neurosarcoidosis.[5] Although the condition is usually unilateral, bilateral facial palsy can occur, presenting with either simultaneous or sequential paralysis. More than half of all patients with facial palsy also have other forms of nervous system involvement. In patients with an isolated facial palsy, the spinal fluid is often normal, but when other manifestations of neurosarcoidosis are present, the CSF is abnormal in 80 percent of patients. The specific cause of facial nerve palsy in sarcoidosis is variable. Rarely, the facial palsy is caused by parotid inflammation. More commonly, the nerve is compromised as it traverses the meninges and subarachnoid space, or facial paresis is due to intra-axial inflammation of the facial nerve motor nucleus. In general, the prognosis for the facial palsy is good, with most patients experiencing recovery of function.

Eighth cranial nerve involvement may affect the auditory or vestibular portions of the nerve. Loss of hearing or vestibular dysfunction may be sudden or insidious and often fluctuates over time. If hearing loss occurs, it is typically of the sensorineural type.[7] As with facial nerve palsy, bilateral eighth nerve disease may occur, and bilateral seventh or eighth nerve dysfunction is suggestive of neurosarcoidosis.

Glossopharyngeal and *vagus nerve* involvement causes dysphagia and dysphonia but is quite uncommon. Hoarseness is more commonly due to laryngeal nerve dysfunction from intrathoracic disease than CNS inflammation involving the vagus nerve.

Eleventh and *twelfth cranial nerve* disease may occur but seems to be rare.

Meningeal Disease

Meningeal disease occurs in approximately 10 to 20 percent of patients with neurosarcoidosis and can present as aseptic meningitis or, less commonly, as a dural-based mass lesion. Aseptic meningitis is characterized by headache, occasional meningismus, and sterile CSF with a mononuclear pleocytosis. Occasionally neutrophils may predominate. Hypoglycorrhachia, or low CSF glucose concentration, is sometimes found, and there is often an elevation of the CSF protein concentration. Oligoclonal bands unique to the CSF may also be present.[6] Postcontrast magnetic resonance imaging (MRI) can delineate the type and extent of meningeal disease, with leptomeningeal involvement being more common than pachymeningeal involvement.[6] Leptomeningitis may have a nodular appearance on postcontrast MRI, and is often focused around the skull base, hypothalamic/pituitary region, and posterior fossa (Fig. 49-6).[6] Pachymeningeal involvement manifests with either mass lesions, or more widespread inflammation. Mass lesions may mimic intracranial tumors such

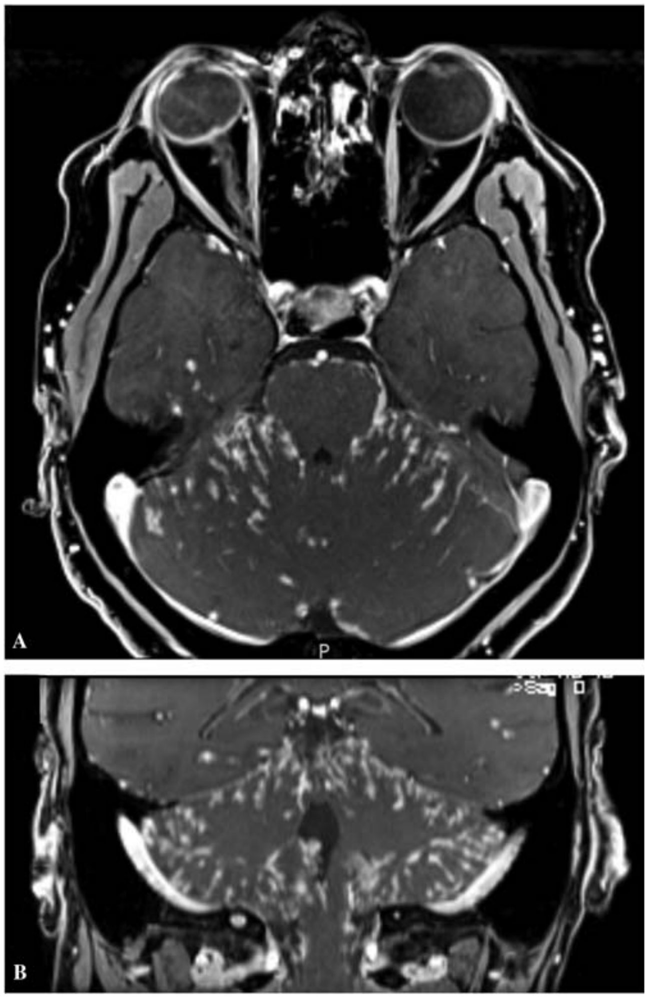

FIGURE 49-6 ■ Cranial MRI. *A*, Axial T1 volumetric interpolated brain examination (VIBE) image with gadolinium. *B*, Coronal T1 VIBE image with gadolinium, showing extensive leptomeningeal enhancement around the cerebellum and infiltrating the fourth ventricle.

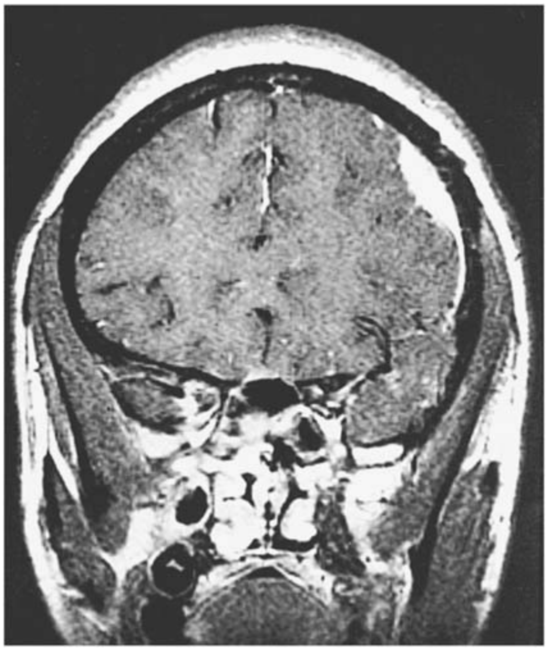

FIGURE 49-7 ▪ Cranial MRI, coronal section, T1-weighted image with gadolinium, demonstrating an enhancing convexity sarcoid mass lesion that was initially mistaken for a meningioma.

as meningiomas (Fig. 49-7), and are often located around basal structures such as the cavernous sinus or orbital apex.[6] It is not uncommon for there to be asymptomatic chronic meningitis within the context of other CNS manifestations of sarcoidosis.

Hydrocephalus

Hydrocephalus is noted in about 10 percent of patients with neurosarcoidosis and may have fatal consequences. Chronic basilar leptomeningitis with obliteration of subarachnoid CSF flow is a major cause of communicating hydrocephalus. In addition, infiltration of the ventricular system by granulomas, granulomatous compression of the aqueduct, or outlet obstruction of the fourth ventricle by granulomas may cause noncommunicating hydrocephalus. Patients with acute hydrocephalus may die suddenly of increased intracranial pressure, and even patients with chronic hydrocephalus have the potential for acute decompensation. Patients with hydrocephalus characteristically present with headache, altered mentation or consciousness, and impaired gait. On examination, papilledema or other signs of raised intracranial pressure may be found. Acute decompensating hydrocephalus is a medical emergency that necessitates prompt diagnosis and treatment. Once clinically suspected, the diagnosis of hydrocephalus is best substantiated with imaging studies, either computerized tomography (CT) or MRI.

Parenchymal Disease

Parenchymal brain disease can present in several forms, and is often associated with overlying meningeal involvement. Hypothalamic dysfunction is the most common manifestation of CNS parenchymal disease.

ENDOCRINE DISORDERS

Any of the neuroendocrinologic systems can be affected by sarcoidosis due to either a hypothalamic or pituitary granulomatous mass or a more diffuse local inflammation. Given the predilection of sarcoidosis for the basal meninges (Fig. 49-8), the relative frequency of such endocrinologic disturbances is not surprising. Anterior pituitary dysfunction is more common than posterior pituitary dysfunction.[8] Potential endocrinologic manifestations include gonadotropin deficiency, TSH deficiency, hyperprolactinemia, and diabetes insipidus.[8] Hypothalamic disorders vary in their effect on vegetative functions. A disorder of thirst is the most common hypothalamic disorder

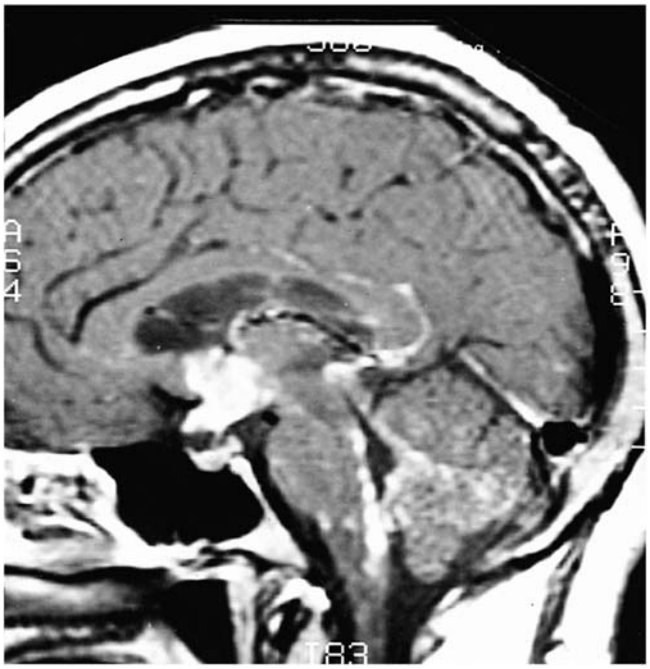

FIGURE 49-8 ▪ Cranial MRI, sagittal section, T1-weighted image with gadolinium, showing hypothalamic and pituitary involvement by sarcoidosis.

related to neurosarcoidosis and is attributed to a change in the hypothalamic osmostat. Less commonly, the syndrome of inappropriate secretion of antidiuretic hormone occurs. Neurosarcoidosis-induced disruptions of hypothalamic–pituitary function can also cause problems with appetite, libido, temperature control, weight regulation, and sleep. Because neuroendocrinologic involvement is relatively common in individuals with CNS sarcoidosis, patients with more than just an isolated facial palsy probably merit a thorough evaluation with specific attention to hypothyroidism, hypocortisolism, hypogonadism, and hyperprolactinemia. Furthermore, in affected patients, contrast-enhanced MRI may identify inflammation of the hypothalamic–pituitary structures or surrounding meninges. Unfortunately, hormonal abnormalities may persist even after effective control of neurosarcoidosis inflammation.[8]

Mass Lesions

An intraparenchymal lesion due to sarcoidosis may present as an isolated mass (Fig. 49-9) in any cerebral area or as multiple cerebral nodules. Such nodules may represent an inflammatory reaction in the Virchow–Robin spaces. Calcifications may be seen, mimicking infection or tumor. Although intraparenchymal mass lesions were historically considered rare in neurosarcoidosis, CT and MRI have shown parenchymal disease to be relatively frequent. The symptoms and signs in individual cases depend on the location of the lesion.

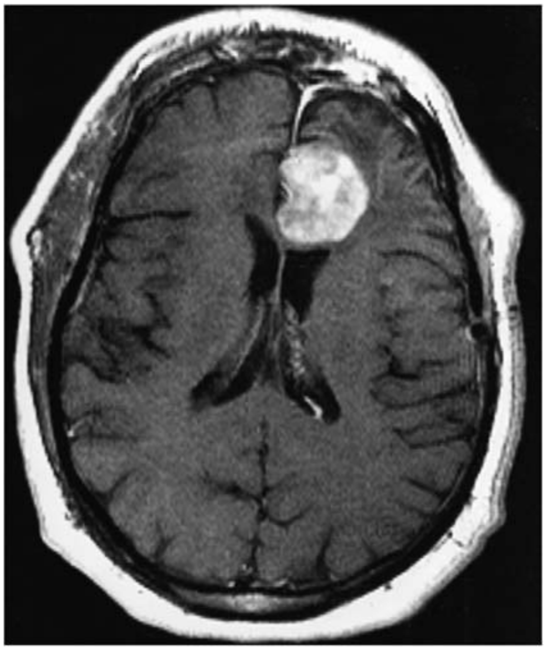

FIGURE 49-9 ■ Cranial MRI, axial section, T1-weighted image with gadolinium, demonstrating a frontal intracerebral mass that was proven by biopsy to be neurosarcoidosis.

Encephalopathy-Vasculopathy and Stroke

The diffuse encephalopathy and vasculopathy associated with neurosarcoidosis are not completely understood. It is often difficult, both clinically and pathologically, to differentiate clearly between these entities and they frequently co-exist. It is best therefore to consider them as a single overlapping entity, while recognizing that, in individual patients, one form or the other may predominate. The clinical presentation of vasculopathy in these patients can also be focal, manifesting with acute stroke.

The diffuse encephalopathy-vasculopathy found in neurosarcoidosis can involve the cerebral hemispheres or the posterior fossa. Patients may experience delirium, personality change, or isolated memory disturbance as a result of focal or diffuse parenchymal inflammation (Fig. 49-10). Clinical findings correlate with the extent of enhancement on imaging studies including hyperintensity on T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI sequences. In these patients,

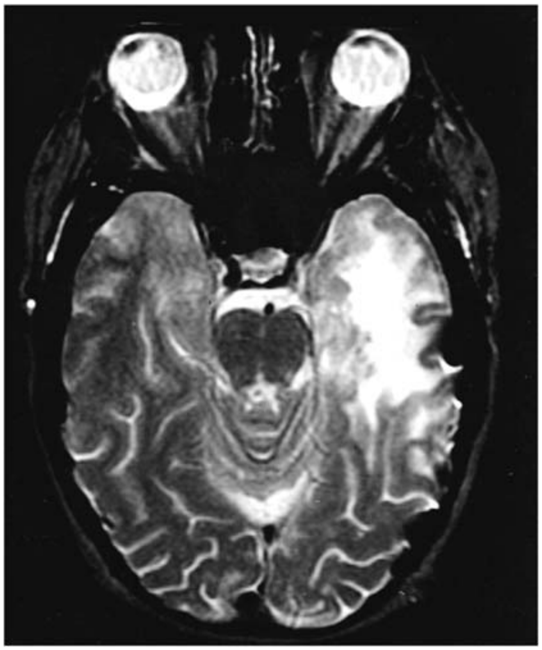

FIGURE 49-10 ■ Cranial MRI, axial section, T2-weighted image, showing a large area of hyperintensity in the temporal lobe that was proven by biopsy to be sarcoidosis manifesting with a focal encephalopathy-vasculopathy.

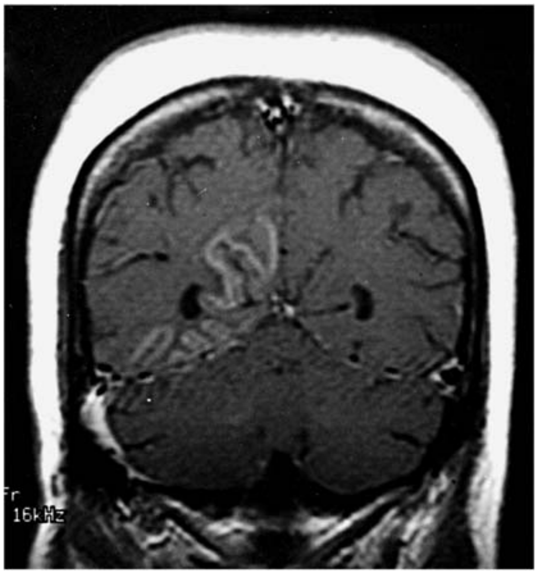

FIGURE 49-11 ■ Cranial MRI, coronal section, T1-weighted image with gadolinium, showing gyral enhancement in the distribution of a posterior cerebral artery branch stroke.

granulomatous inflammation is thought to infiltrate the brain parenchyma via perivascular spaces surrounding small and medium-sized arteries and veins.[9] Granulomas may also extend through the vessel walls, resulting in granulomatous arteritis (Fig. 49-11).

Transient ischemic attacks and ischemic and hemorrhagic stroke due to neurosarcoidosis have all been described. Stroke can occur due to thrombotic occlusion of a vessel secondary to perivascular inflammation, or by extension of granulomas through the vessel wall.[2,9] Ischemic infarcts frequently occur in small or medium-sized vessel territories (sometimes associated with perivascular enhancement seen on MRI), and multiple infarcts in individual patients are common.[2,9] Large-vessel ischemic strokes are more likely to result from compressive perivascular mass lesions, emboli from sarcoidosis-associated cardiomyopathy, or resultant cardiac arrhythmias. Venous infarctions or cerebral venous sinus thrombosis can also occur, and are likely related to phlebitis, which has been identified pathologically and radiologically in neurosarcoidosis. Hemorrhagic stroke may occur from an arterial or venous source, and asymptomatic microhemorrhages can also be seen on MRI.[2] Patients with stroke secondary to neurosarcoidosis are often encephalopathic, likely due to co-existing meningeal enhancement or hydrocephalus.[2,9] Neurosarcoidosis manifesting with stroke may be associated with substantial disability and mortality.[9]

SEIZURES

Seizures may be a manifestation of CNS parenchymal disease due to neurosarcoidosis. They may be focal or generalized and portend a relatively poor prognosis, reflecting the concurrence of severe CNS parenchymal disease or hydrocephalus. Seizures in patients with neurosarcoidosis are relatively easy to control when the underlying CNS inflammatory process is treated effectively.

MYELOPATHY

Spinal cord sarcoidosis may manifest as intramedullary, intradural but extramedullary, or extradural granulomatous masses. Intramedullary spinal cord disease can present with a myelitis that is analogous to the cerebral encephalopathy-vasculopathy described earlier. MRI typically demonstrates a longitudinally extensive spinal cord lesion with dorsal enhancement contiguous with the surface of the cord, sometimes termed “subpial enhancement” (Fig. 49-12).[10] When enhancement is also present in the central canal, the pattern may resemble a trident-head. Intraspinal mass lesions due to sarcoidosis may have a tumefactive appearance on MRI, with associated subpial or leptomeningeal enhancement.[11] In addition, sarcoidosis may present as a radiculopathy, polyradiculopathy, or cauda equina syndrome. Spinal arachnoiditis sometimes occurs. Spinal cord sarcoidosis may appear in late stages as focal spinal cord atrophy.

Peripheral Neuropathy

Large-fiber peripheral neuropathy in neurosarcoidosis may take the form of a chronic sensorimotor, pure motor, or pure sensory polyneuropathy; mononeuritis multiplex; or an acute demyelinating polyneuropathy. The neuropathy usually occurs without CNS involvement. The most common form of large-fiber neuropathy in neurosarcoidosis is a chronic sensorimotor polyneuropathy of axonal type. This condition typically begins months to years following an initial diagnosis, but in some instances, symptoms precede the discovery of systemic disease. The neuropathy is usually mild and classically manifests with distal paresthesias, decreased vibration and proprioception, and reduced ankle reflexes. Large-fiber neuropathy in sarcoidosis has been attributed to epineurial and perineurial granulomas with or without an associated

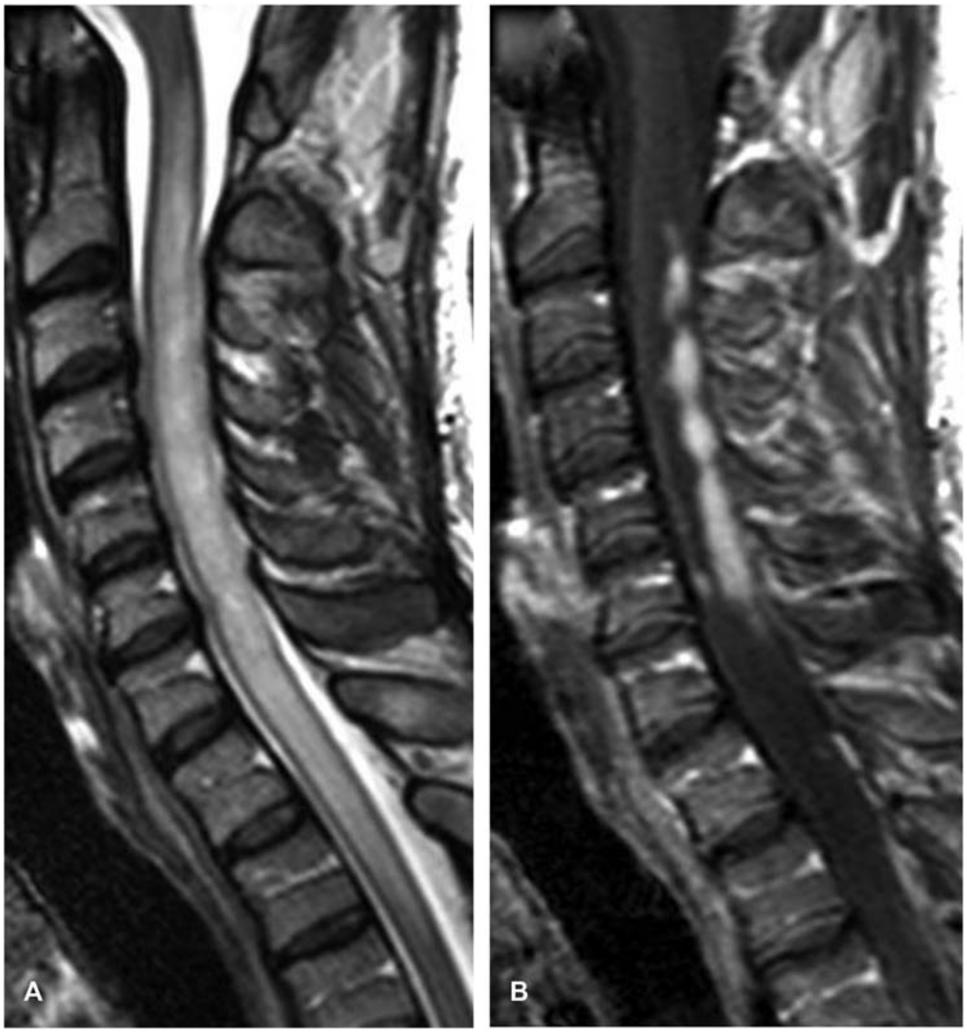

FIGURE 49-12 ■ Spinal MRI. *A*, Sagittal T2. *B*, Sagittal T1 with gadolinium, demonstrating longitudinally extensive myelitis with posterior enhancement due to sarcoidosis.

granulomatous vasculitis, producing axonal degeneration with associated demyelination. Endoneurial granulomas may also occur and are associated with primary segmental demyelination in patients with sensorimotor neuropathy. Nerve damage may be due to granulomatous vasculitis, the compressive effects of granulomas, or the local effects of inflammation.

Sarcoidosis-associated small-fiber sensory neuropathy is actually much more common than large-fiber neuropathy.[12] Small-fiber neuropathy in sarcoidosis manifests with pain and paresthesia, associated with impaired pain and temperature appreciation and variable autonomic dysfunction. However, small-fiber neuropathy occurs in the absence of pathologic evidence of granulomas in the skin or peripheral nerves and is not necessarily associated with other manifestations of neurosarcoidosis—therefore the pathophysiology is unclear. It is possible that the neuropathy is a response to inflammatory mediators, especially tumor necrosis factor alpha (TNF-α). Patients with sarcoidosis may have other risk factors for small-fiber neuropathy, including metabolic syndrome or diabetes mellitus secondary to corticosteroid treatment.[12]

Myopathy

Manifestations of sarcoidosis myopathy, although rare, include acute, subacute, or chronic weakness; fatigue; myalgia; muscle atrophy; and palpable muscle nodules. Severe muscle disease can result in fibrosis and contractures. Sarcoidosis may also manifest with myositis, muscle atrophy, or occasional pseudohypertrophy. Sometimes concomitant neuropathy is detected.

Muscle involvement by noncaseating granulomas can be demonstrated with muscle biopsy and is frequently asymptomatic. Differentiating between sarcoidosis myopathy, polymyositis, dermatomyositis, and inclusion body myositis may be difficult, and it is important to evaluate other organ systems carefully for evidence of sarcoidosis.

DIFFERENTIAL DIAGNOSIS

Diagnostically, two common clinical situations occur with neurosarcoidosis. In the first, a patient without established sarcoidosis has a clinical picture suggestive of neurosarcoidosis; the major goal is then to establish the presence of systemic sarcoidosis. In the second, a patient with already established systemic sarcoidosis develops neurologic symptoms, and it is then necessary to confirm that the neurologic problem is due to neurosarcoidosis rather than another cause.

Presence of Systemic Sarcoidosis

When a patient without documented systemic sarcoidosis develops a clinical syndrome suggestive of neurosarcoidosis, histologic evidence of sarcoidosis should be sought in other organ systems (Table 49-1). Sarcoidosis most frequently affects the intrathoracic structures (87% of patients), followed by lymph node, skin, and ocular involvement. Since corticosteroid therapy may mask signs of systemic disease, treatment should be postponed, if possible, while a search for systemic disease is initiated.

Pulmonary involvement is so common in sarcoidosis that this possibility should be considered first when attempting to establish the presence of systemic sarcoidosis unless there is obvious skin disease or palpable lymphadenopathy. Evidence to support pulmonary involvement can be obtained from chest radiographs or CT scans and pulmonary function testing, including lung diffusion capacity. When these studies suggest pulmonary or intrathoracic lymph node involvement, transbronchial or mediastinal biopsy can be used to confirm the diagnosis.

Other sites of involvement of systemic disease can be considered for biopsy on the basis of clinical assessments including the nasosinus mucosa, conjunctiva, lacrimal glands, liver, and muscle. A thorough ocular examination is indicated to search for uveitis, retinal periphlebitis, or superficial lesions for biopsy. Other ocular findings in sarcoidosis include iritis, retinal lesions (granulomas, vascular occlusions, and chorioretinitis), and optic disc pathology (edema, granulomatous nodules, and atrophy).

Gallium-67 scanning had previously been promoted as a valuable imaging method for the detection of systemic sarcoidosis, but current experience indicates that fluorodeoxyglucose positron emission tomography (PET) scanning is more sensitive for highlighting regions of increased metabolic activity due to sarcoidosis. Although increased activity on PET scans can represent neoplasia or infection as well as granulomatous inflammation, when used in the proper context, PET scanning can be a valuable tool for targeting biopsy. Furthermore, PET scanning may be useful in assessing organ involvement in sarcoidosis and even monitoring therapeutic response.

Various laboratory measures may be abnormal in sarcoidosis including increased serum ACE level; increased serum gamma globulins; hematologic abnormalities such as anemia, leukopenia, and thrombocytopenia; and metabolic derangements such as hypercalcemia, hypercalciuria, and hepatic and renal dysfunction. None is highly specific for sarcoidosis, but the most specific is the serum ACE level. Serum ACE is thought to be produced by alveolar macrophages and epithelioid giant cells and, in effect, reflects the “granulomatous load” of a patient. However, neither serum nor CSF ACE is highly sensitive, with just 50 to 60 percent of patients with active sarcoidosis showing abnormalities, nor very specific, because it is also often elevated in patients with other conditions. Therefore, its utility in the diagnosis or monitoring of sarcoidosis has essentially been superseded by imaging studies in recent years.

Diagnosis of Neurosarcoidosis

Patients with well-documented systemic sarcoidosis who develop neurologic disease merit careful appraisal to exclude causes other than sarcoidosis for their neurologic problem. Neurosarcoidosis can be confused with many other neurologic diseases and, because it is often not possible or judicious to biopsy affected tissue from the nervous system, the diagnosis may need to be made on purely clinical grounds.

Consideration must be given to disease entities that may mimic neurosarcoidosis, particularly infection and neoplasia. Once such disorders have been excluded, treatment for neurosarcoidosis can be instituted. When the response to treatment is disappointing, the diagnosis of neurosarcoidosis should be reviewed and a more extensive evaluation, including nervous system biopsy, contemplated to exclude other causes of symptoms and signs.

Brain imaging studies can be particularly helpful in neurosarcoidosis, and MRI with contrast is the preferred technique. T2-weighted and FLAIR sequences may demonstrate parenchymal disease while postcontrast T1 or FLAIR sequences may demonstrate pachymeningeal or leptomeningeal enhancement (Figs. 49-6 and 49-13), cranial nerve enhancement, or parenchymal enhancement (Figs. 49-8 and 49-9). Enhancement presumably reflects a breakdown of the blood–brain barrier and implies active inflammation; hence, the presence of enhancement is frequently used as a biomarker of treatment response in clinical practice. MR angiography may demonstrate abnormalities in patients with vasculopathy.[9] Spinal MRI in patients with myelopathy may reveal meningeal or intramedullary disease with focal or diffuse enhancement (Fig. 49-12) or atrophy.[10] Enhancing nodules or thickened or matted nerve roots may be appreciated in the cauda equina.

CSF analysis is frequently helpful; most patients with CNS sarcoidosis have some CSF abnormality, and patients with leptomeningeal involvement demonstrate the most marked abnormalities.[6] Reported abnormalities include an elevated CSF pressure, a high protein level, hypoglycorrhachia, elevated albumin CSF/serum quotient, and a usually predominantly mononuclear pleocytosis (occasionally neutrophilic), with up to several hundred cells per mm^3. In addition, some patients have oligoclonal bands in the CSF or an elevated immunoglobulin G index. None of these abnormalities is specific for neurosarcoidosis.

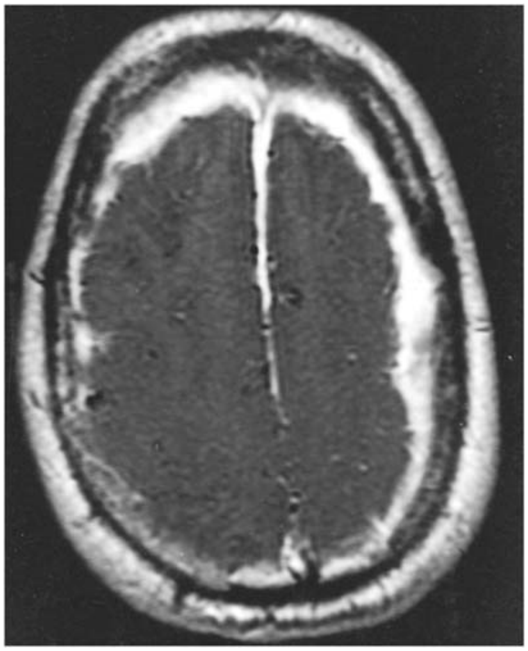

FIGURE 49-13 ■ Cranial MRI, axial view, T1-weighted image, with gadolinium, demonstrating marked dural enhancement due to sarcoidosis.

The CSF level of ACE activity tends to be raised in some patients with CNS sarcoidosis, although abnormalities are also seen in the presence of infection and malignancy. CSF ACE is thought to be produced by CNS granulomas, especially those near the meninges, and historically was used in the diagnostic evaluation of neurosarcoidosis. However, because of limited sensitivity and specificity, assay of CSF ACE activity is no longer recommended.

Visual evoked potentials (VEPs) or optical coherence tomography can reveal abnormalities of the anterior visual pathway in neurosarcoidosis. These studies are often abnormal in patients with symptomatic optic nerve disease and may be abnormal in some patients with CNS sarcoidosis but no clinical evidence of optic nerve dysfunction. Similarly, brainstem auditory evoked potentials (BAEPs) are often abnormal in patients with brainstem or eighth nerve symptoms and may be abnormal in neurologically ill patients without overt disease in these areas. Somatosensory evoked potentials have not been comprehensively studied in the assessment of patients with sarcoidosis; preliminary evidence suggests that their clinical utility is similar to that of VEPs and BAEPs in confirming the involvement of a specific sensory system.

Nerve conduction studies (NCSs) in patients with sarcoidosis-associated large-fiber neuropathy usually reveal changes compatible with an axonal neuropathy, although slowing is sometimes more pronounced and suggestive of demyelination. Electromyography may show denervation in patients with a neuropathy or radiculopathy and may demonstrate myopathic changes in patients with a symptomatic myopathy. Patients with sarcoidosis-associated small-fiber neuropathy typically have normal NCS but may have abnormalities on quantitative sensory (temperature threshold testing) and autonomic testing and a decreased number of small fibers in cutaneous nerves on skin biopsy of the extremities. MRI of muscles in myopathic patients is usually abnormal, sometimes showing a characteristic "star-shaped" pattern of muscle nodules. Muscle or nerve biopsy can be informative and muscle biopsy can be targeted to areas of MRI enhancement.

TABLE 49-3 ■ Diagnostic Criteria for Neurosarcoidosis

Diagnostic Certainty	Description
Possible neurosarcoidosis	1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system and after rigorous exclusion of other causes 2. There is no pathologic confirmation of granulomatous disease
Probable neurosarcoidosis	1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes 2. There is pathologic confirmation of systemic granulomatous disease consistent with sarcoidosis
Definite neurosarcoidosis	1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes 2. The nervous system pathology is consistent with neurosarcoidosis Type a. Extraneural sarcoidosis is evident Type b. No extraneural sarcoidosis is evident (isolated CNS sarcoidosis)

MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; EMG/NCS, electromyography/neuroconduction studies.

The diagnosis of sarcoidosis is most secure when it is based on pathology and when more than one organ system is involved. However, since tissue from the nervous system is difficult to secure for pathologic analysis and other tests are not diagnostic of neurosarcoidosis, the diagnosis must sometimes remain tentative despite all efforts. In considering a diagnosis of neurosarcoidosis, it is useful to grade its likelihood. Consensus diagnostic criteria were outlined by the Neurosarcoidosis Consortium Consensus Group in 2018 and are outlined in Table 49-3.[13]

Isolated Neurosarcoidosis

In some patients with a clinical syndrome suggestive of neurosarcoidosis along with supportive neuroimaging, CSF, or electrophysiologic findings, extensive investigation may reveal no evidence of underlying symptomatic or asymptomatic systemic sarcoidosis. This condition is termed "isolated neurosarcoidosis" and may occur in 4 to 10 percent of cases of neurosarcoidosis.[6] Nervous system biopsy in such patients may confirm the presence of granulomatous inflammation. However, in certain cases the risks of nervous system biopsy may be considered too high, for example with involvement of the spinal cord or brainstem structures. In these cases of suspected isolated neurosarcoidosis without biopsy confirmation, empiric treatment may be appropriate with close clinical monitoring and reassessment of the differential diagnosis according to clinical evolution and treatment response.

TREATMENT

No rigorous studies compare the various treatments for neurosarcoidosis. Although corticosteroid therapy is the mainstay of treatment, decisions regarding the optimal therapeutic dose and duration of therapy are made on an individual basis. A suggested treatment paradigm is shown in Fig. 49-14.

Treatment with corticosteroids is widely accepted and recommended for all forms of neurosarcoidosis. Many individual case reports and series provide evidence that it can produce impressive responses and alleviate symptoms, at least on a short-term basis. The theoretical goal of corticosteroid treatment in neurosarcoidosis is to reduce granulomatous inflammation, therefore diminishing the irreversible fibrosis and neuroaxonal damage that can develop, and to minimize tissue ischemia from perivascular inflammation. Corticosteroid treatment is often commenced at relatively high doses and tapered as the inflammatory process recedes. The decision to introduce other immunomodulating or immunosuppressive agents is frequently complex and should be based on individual factors.

Neurosarcoidosis can follow either a monophasic or chronic/recurrent course, and certain manifestations may be more likely to follow a monophasic course, such as isolated cranial neuropathy. Patients with multiple areas of neurologic involvement may be deemed more likely to require medium- to long-term immunotherapy. Parenchymal disease of the brain or spinal cord is often treated more aggressively than nonparenchymal disease due to higher risks of disability accumulation.[14]

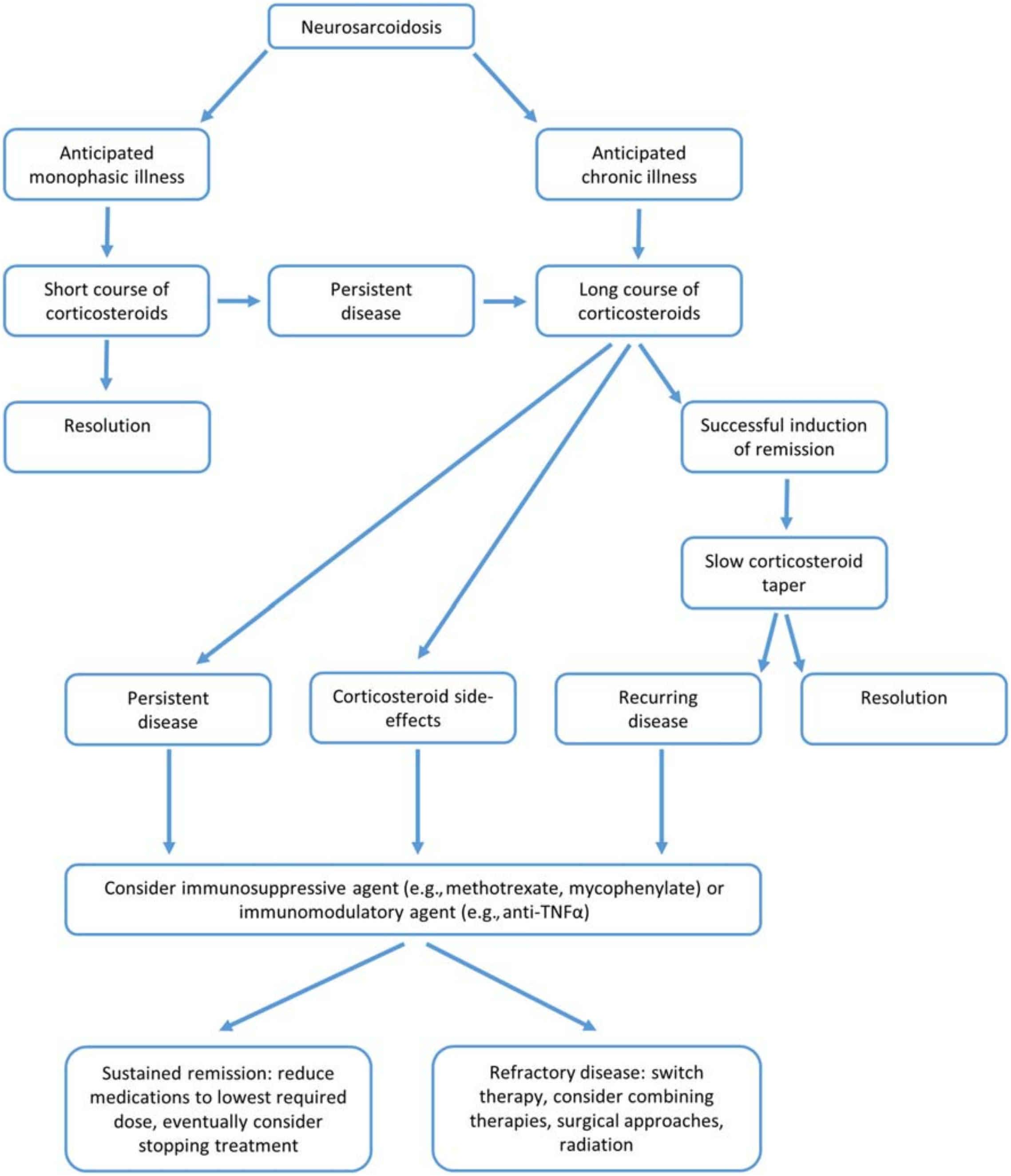
Neurosarcoidosis
Anticipated monophasic illness
Anticipated chronic illness
Short course of corticosteroids
Persistent disease
Long course of corticosteroids
Resolution
Successful induction of remission
Slow corticosteroid taper
Persistent disease
Corticosteroid side-effects
Recurring disease
Resolution
Consider immunosuppressive agent (e.g., methotrexate, mycophenylate) or immunomodulatory agent (e.g., anti-TNFα)
Sustained remission: reduce medications to lowest required dose, eventually consider stopping treatment
Refractory disease: switch therapy, consider combining therapies, surgical approaches, radiation

FIGURE 49-14 ■ Treatment paradigm for patients with neurosarcoidosis.

Patient comorbidities such as cancer or obesity may impact therapeutic decision-making. Patients with active systemic sarcoidosis may have other areas of organ involvement influencing therapeutic choices.

Cranial Neuropathy

PERIPHERAL FACIAL PALSY

Facial weakness may improve without any specific treatment, and the long-term prognosis for patients seems favorable. A controlled trial of treatment has not been performed; however, it seems reasonable to give a short course (2 to 4 weeks) of prednisone in patients without other neurosarcoidosis manifestations. For the first week, the recommended dosing is in the range of 0.5 to 1.0 mg/kg daily or 40 to 60 mg daily. This initial dosing is followed by a gradual reduction leading to discontinuation of prednisone over the subsequent weeks. General supportive care including protection from corneal abrasions, as for any patient with a peripheral facial palsy, should be provided.

OTHER CRANIAL NERVE PALSIES

Patients with other cranial neuropathies may be managed with a corticosteroid protocol similar to that for peripheral facial palsy. However, often more than 4 weeks of therapy is needed. In particular, patients with optic neuropathy or dysfunction of the eighth cranial nerve may need more prolonged, aggressive therapy, which may not prevent irreversible nerve damage.

Aseptic Meningitis

Aseptic meningitis is typically initially treated with corticosteroids, often with a short course of high-dose intravenous methylprednisone followed by tapering oral prednisone. When planning the dose and duration of corticosteroid treatment, the chronicity and severity of the clinical manifestations should be considered, as well as the extent of meningeal enhancement seen on MRI. Patients with relatively mild, acute presentations may respond to a short (2- to 4-week) course of prednisone. In patients with chronic symptoms or associated other neurologic manifestations (such as hydrocephalus or cranial nerve palsies), a longer course of corticosteroid treatment with a slow taper over months may be required. In these patients, meningitis may recur during the corticosteroid taper, often prompting consideration of additional therapeutic options such as a corticosteroid-sparing agent. Response to treatment can be assessed by interval evaluations of meningeal enhancement on MRI or CSF pleocytosis in addition to clinical examination. However, the goal of therapy for chronic aseptic meningitis is not necessarily complete clearing of an asymptomatic CSF pleocytosis as attempts to completely normalize the CSF may expose patients to the adverse side effects of corticosteroids or other therapeutic agents without evidence of benefit in patients who are otherwise asymptomatic.

Hydrocephalus

Treatment of hydrocephalus in neurosarcoidosis varies depending on the cause and severity of the hydrocephalus. Mild, symptomatic hydrocephalus associated with meningeal disease may respond to corticosteroid treatment; prolonged therapy is often appropriate. Life-threatening, corticosteroid-resistant or acute obstructive hydrocephalus (e.g., secondary to a granulomatous mass lesion) requires external ventricular drainage or ventricular shunting. Unfortunately, mild hydrocephalus may evolve to severe, life-threatening disease quite rapidly; therefore, patients and care providers should be well educated as to the symptoms of acute progressive hydrocephalus and know to obtain prompt emergency care. High-dose intravenous corticosteroid therapy (methylprednisolone 20 mg/kg per day for 3 days) sometimes stabilizes a patient with life-threatening hydrocephalus, but urgent ventricular drainage is usually necessary. Shunt placement is not without risk in this patient population, which is the reason that prophylactic shunting in asymptomatic patients with hydrocephalus is not advocated. Shunt obstruction is quite common, and placement of a foreign object in the CNS of an immunosuppressed host predisposes to infection. As in all cases of hydrocephalus, a careful neuroimaging assessment should be completed before lumbar puncture is undertaken, to assess whether the procedure is safe.

Parenchymal Disease

Corticosteroid therapy may improve patients with a diffuse encephalopathy-vasculopathy syndrome or CNS mass lesion. Only rarely, however, does immunosuppressive treatment improve neuroendocrine dysfunction.[8]

Corticosteroid treatment of CNS parenchymal disease and other severe neurologic manifestations of sarcoidosis usually starts with prednisone, 1.0 to 1.5 mg/kg daily. Critically ill patients may require high-dose intravenous corticosteroid therapy. A short course of methylprednisolone, 20 mg/kg daily intravenously for 3 days, followed by prednisone, 1.0 to 1.5 mg/kg daily for 2 to 4 weeks, is a typical regimen. Patients with parenchymal disease often require prolonged therapy due to risks of progressive or recurrent disease, and prednisone should thus be tapered slowly, for example, by 5-mg decrements every 2 weeks as the clinical course is monitored.[14] Neurosarcoidosis often worsens at a prednisone dose of 10 mg or less daily.

Once a daily prednisone dose of approximately 10 mg is achieved, the patient should be evaluated for evidence of worsening or recurring disease. Clinical disease can be monitored by symptoms and examination, but surveillance of subclinical disease of the CNS involves neuroimaging. Intense enhancement of the meninges or parenchyma, for example, suggests that neurosarcoidosis is active, and further decreases in the corticosteroid dose may lead to a clinical exacerbation. Other manifestations of neurosarcoidosis can be evaluated for subclinical deterioration on an individualized basis (e.g., by evaluating NCS or serum creatine kinase level), but persistent mild CSF abnormalities are usually not an indication for continuing or escalating corticosteroid therapy. If neurosarcoidosis appears quiescent, a low daily prednisone dose of about 10 mg can be tapered further by 1 mg every 2 to 4 weeks. If a patient has a clinical relapse, the dose of prednisone should be doubled unless the dose is very modest, in which case a prednisone dose of 10 to 20 mg daily can be prescribed; the patient should then be observed for approximately 4 weeks before another taper is contemplated. Patients may require multiple cycles of higher and lower corticosteroid dosing during attempts to taper medications. Since the disease may become quiescent, patients may be needlessly exposed to the harmful side effects of long-term, high-dose corticosteroids if attempts are not made to withdraw medication. Additional treatments such as corticosteroid-sparing agents should be considered in patients with recurrent disease, chronically active disease, or persistently high corticosteroid requirements.

Seizures are generally not a major limiting problem and can usually be well controlled with antiseizure medications if the underlying CNS inflammatory reaction is treated effectively. Seizures are an indication of, or marker for, the presence of parenchymal involvement of the brain.

In patients with a CNS mass lesion that is unresponsive to high-dose corticosteroids, surgical resection may be considered, especially in life-threatening situations.

Peripheral Neuropathy and Myopathy

Patients with large-fiber peripheral neuropathy or myopathy may respond to a several-week course of corticosteroids, usually beginning with oral prednisone, 1 mg/kg per day (or approximately 60 mg/day). Here, too, prolonged treatment may be indicated, and corticosteroids should be tapered slowly, as discussed earlier. As small-fiber neuropathy is not thought to be directly caused by granulomatous inflammation of the nerves, it is unclear whether it should be considered as a target for treatment, or whether treatment in these patients should simply aim to control other manifestations of sarcoidosis. However, symptomatic improvements have been reported in patients with small-fiber neuropathy treated with intravenous immunoglobulins or anti-TNF-α agents, and with ARA290 (an erythropoietin derivative thought to have anti-inflammatory properties).[12] Symptomatic treatment, such as neuropathic pain medications, should also be considered in these patients.

IMMUNOSUPPRESSIVE AND IMMUNOMODULATORY TREATMENTS

Treatment alternatives to corticosteroids are increasingly considered for patients with neurosarcoidosis (Fig. 49-14). Indications for their use include contraindications to corticosteroids as initial therapy, chronic adverse effects of corticosteroids, an anticipated chronic course requiring high doses of corticosteroids, and progressive disease activity despite corticosteroid therapy. In general, exposing patients to high doses of corticosteroids over prolonged periods should be avoided. Medications that have been used as alternatives or adjuncts to corticosteroids include immunosuppressive agents such as mycophenolate mofetil, azathioprine, methotrexate, cyclophosphamide, chlorambucil, cladribine (2-chlorodeoxyadenosine), and monoclonal antibodies such as anti-TNF-α agents. While many of these agents are commonly used in clinical practice, the literature on their use in neurosarcoidosis is limited to case series or retrospective observational studies, rather than randomized-controlled trials.

The addition of other immunotherapy may allow a gradual decrease in corticosteroid dosage to prevent or minimize corticosteroid complications, often without deterioration in the patient's clinical status. However, in patients with a chronic or recurrent disease course, corticosteroids can rarely be eliminated completely, and low doses of corticosteroids may be required long-term to maintain disease control. In a small proportion of patients, neurosarcoidosis may be highly refractory to multiple treatments. The potential adverse effects of the therapy and extent of systemic disease should determine the choice of alternative treatment. It is wise to choose an agent whose adverse effects spare an organ or organ system that may already be compromised. In general, the side effects of these medications are limited, predictable, and respond to withdrawal of the offending agent. It may even be possible to restart the medication in some cases, without recurrent side effects.

Because TNF-α is implicated in the pathogenesis of granulomatous inflammation, TNF-α antagonists such as infliximab and biosimilar agents have been used with success for refractory neurosarcoidosis, with accruing evidence for the utility of these agents.[15] With retrospective studies suggesting favorable outcomes in patients treated with TNF-α antagonists, these medications are increasingly being employed in the initial treatment of neurosarcoidosis in conjunction with corticosteroids and mycophenolate or methotrexate to treat severe CNS disease. Rituximab, a monoclonal antibody directed against B cells, has also been beneficial in some case reports.

Another option for some patients with refractory CNS sarcoidosis is radiation therapy. The small number of reported patients treated in this manner precludes definitive conclusions about efficacy. Some case reports suggest a beneficial response, especially if total nodal and craniospinal irradiation is performed. A total dose of 19.5 Gy with daily fractionation of 1.5 Gy has been suggested. It appears that although radiation therapy is sometimes of benefit, continued immunosuppressive therapy is usually necessary.

Although it is not possible to predict with absolute certainty which patients with neurosarcoidosis will have disease refractory to conventional corticosteroid treatment, certain patients may have a particularly high-risk clinical profile. Patients with an optic neuropathy or CNS parenchymal disease (e.g., mass lesions, extensive encephalopathy-vasculopathy, or myelopathy) are at especially high risk. Such patients might benefit from the prompt use of adjunctive alternative treatments or if they either become refractory to corticosteroids or develop intolerable side effects. If a patient is stable for several months on low-dose prednisone and an alternative treatment, slow tapering of one of the drugs can be considered.

GENERAL SUPPORTIVE CARE

Patients with neurosarcoidosis, particularly those receiving treatment with potent immunosuppressive agents, require close attention to their general medical well-being, including monitoring for potential adverse effects of treatment. Formal, prescribed exercise and dietary advice may help patients avoid the weight gain and deconditioning associated with corticosteroid treatment. Rehabilitation services should be utilized as appropriate. Depression is not uncommon, and treatment is often helpful. Fatigue and cognitive symptoms are also common. Sleep disorders, especially sleep apnea, should be considered as a cause of fatigue or cognitive decline.

Therapy for endocrinologic disturbances is important. In particular, hypothyroidism, especially hypothalamic hypothyroidism, and hypogonadism are major problems in neurosarcoidosis that often require therapy. Patients receiving protracted, low-dose corticosteroid regimens may require supplemental doses of corticosteroids during periods of intercurrent illness or stress. Diabetes mellitus is a potential side effect of long-term, high-dose corticosteroid treatment but usually is not associated with ketoacidosis. Exercise and dietary programs are useful in managing hyperglycemia, but oral hypoglycemic agents or insulin therapy may be needed.

Patients with sarcoidosis are at risk for osteoporosis, especially from corticosteroid therapy. The treatment of osteoporosis in this context is a challenge because sarcoidosis may cause hypercalcemia and hypercalciuria. Management requires reduction of corticosteroid dosage when possible, cautious use of supplements of calcium and vitamin D, hormonal treatment, and use of other bone-building agents. Screening and serial measurements of bone density may be useful.

Patients with refractory neurosarcoidosis are at risk from both the sarcoidosis-associated inflammatory process and the complications of various therapies. If a patient is not doing well, not only should the original diagnosis of sarcoidosis be questioned, but the patient should also be evaluated for additional complications such as infection and malignancy.

PROGNOSIS

The clinical course and prognosis of neurosarcoidosis vary, but are somewhat predictable. One-third to two-thirds of patients will have a monophasic neurologic illness, and the remainder will have a chronically progressive or recurring course. Those with a monophasic illness typically have an isolated cranial neuropathy, most often involving the facial nerve, or an episode of aseptic meningitis. Those with a chronic course usually present with CNS parenchymal disease, hydrocephalus, multiple cranial neuropathies (especially involving the optic or vestibulocochlear nerve), peripheral neuropathy, or myopathy. Patients with CNS parenchymal disease or hydrocephalus are at highest risk of death, from either the inflammatory process itself or complications of therapy. Historically, mortality with neurosarcoidosis has been reported as approximately 5 to 10 percent, but more recent experience with new advances in treatment suggest that the mortality is in the lower range of that estimate.[5]

Because most patients with neurosarcoidosis are treated with immunosuppressive agents, it is impossible to determine the natural history of the untreated disorder. There is a lack of data demonstrating how treatment impacts the long-term profile of the disease, however it is thought that reducing inflammation-induced neuroaxonal or vasculopathic damage probably improves outcomes similar to other neuroinflammatory and neuroimmune disorders such as multiple sclerosis or autoimmune encephalitis. Even in severely ill or impaired patients, the inflammatory process may spontaneously subside over time, but other patients with recurrent or progressive disease can become severely incapacitated even with aggressive treatment.

In monitoring the response to treatment, a target measure, such as a specific clinical sign, symptom, functional assessment, or neurodiagnostic test, should be defined. For instance, a timed walk can be used for clinical assessment in some patients with gait disturbance from myelopathy or myopathy; in patients with meningeal or parenchymal disease, contrast-enhanced MRI is a helpful measure. This type of focused approach can be used to judge a response over a relatively short period of time.

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CHAPTER

50

Connective Tissue Diseases, Vasculitis, and the Nervous System

JOHN C. PROBASCO

CONNECTIVE TISSUE DISEASES

- Systemic Lupus Erythematosus
  - *Systemic Disease*
  - *Neuropsychiatric Systemic Lupus Erythematosus*
  - *Peripheral Nervous System Disease*
  - *Treatment*
- Sjögren Syndrome
  - *Systemic Disease*
  - *Central Nervous System Disease*
  - *Peripheral Nervous System Disease*
  - *Treatment*
- Systemic Sclerosis
  - *Systemic Disease*
  - *Central Nervous System Disease*
  - *Peripheral Nervous System Disease*
  - *Treatment*
- Rheumatoid Arthritis
  - *Systemic Disease*
  - *Central Nervous System Disease*
  - *Peripheral Nervous System Disease*
  - *Treatment*
- Myopathies in Connective Tissue Disease

VASCULITIS

- Primary Vasculitides of the Nervous System
  - *Primary Vasculitis of the Central Nervous System*
  - *Nonsystemic Vasculitic Neuropathy*
- Systemic Vasculitis
  - *Systemic Disease*
  - *Central Nervous System Disease*
  - *Peripheral Nervous System Disease*
  - *Treatment*
- Polymyalgia Rheumatica and Giant-Cell Arteritis
  - *Systemic Disease*
  - *Central Nervous System Disease*
  - *Peripheral Nervous System Disease*
  - *Treatment*
- Takayasu Arteritis
  - *Systemic Disease*
  - *Central Nervous System Disease*
  - *Treatment*
- Behçet Disease
  - *Systemic Disease*
  - *Central Nervous System Disease*
  - *Peripheral Nervous System Disease*
  - *Treatment*

The systemic inflammatory disorders discussed in this chapter can manifest with diverse neurologic syndromes due to central, peripheral, and autonomic nervous system involvement. These presentations can be in isolation or coincident, sequential or simultaneous. Patients can also develop neurologic syndromes secondary to the treatment of systemic inflammatory disease. Here, we discuss the connective tissue disorders and vasculitides that commonly have neurologic manifestations as well as differential diagnostic considerations.

CONNECTIVE TISSUE DISEASES

Systemic Lupus Erythematosus

SYSTEMIC DISEASE

Systemic lupus erythematosus (SLE) is a common systemic autoimmune disease with up to 150 cases per 100,000 population worldwide. SLE can manifest with a wide spectrum of systemic and neurologic findings and symptoms, each with varying severity. The 10-year mortality rate of SLE is about 30 percent. Proposed

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diagnostic criteria have undergone multiple revisions to improve sensitivity and specificity. In 2019, the European League Against Rheumatism and the American College of Rheumatology (EULAR/ACJR) jointly released updated, validated classification criteria for SLE, incorporating weighted criteria (Table 50-1).[1] In the

TABLE 50-1 ■ 2019 European League Against Rheumatism and the American College of Rheumatology (EULAR/ACJR) Classification Criteria for Systemic Lupus Erythematosus (SLE)

Domain	Item	Definition	Weighted Points
Entry criterion	Positive ANA	$>$1:80 by Hep-2 Immunofluorescence	Mandatory
Constitutional	Fever	Temperature $\geq$38.3°C	2
Hematologic	Leukopenia	White blood cell count $<$4,000/mm^3	3
	Thrombocytopenia	Platelet count $<$100,000/mm^3	4
	Autoimmune hemolysis	Evidence of hemolysis (e.g., reticulocytosis) AND positive Coombs test	4
Neuropsychiatric	Delirium	(1) Change in consciousness or level of arousal with reduced ability to focus; (2) symptom development over hours to $<$2 days; (3) syndrome fluctuation throughout the day; and either (4a) acute/subacute change in cognition or (4b) change in behavior, mood, or affect	2
	Psychosis	(1) Delusions and/or hallucinations without insight; (2) absence of delirium	3
	Seizure	Primary general or focal seizure	5
Mucocutaneous	Alopecia		2
	Oral ulcers		2
	SCLE/DLE	Subacute cutaneous lupus erythematosus (SCLE): annular or papulosquamous cutaneous eruption which is usually photodistributed; skin biopsy with typical changes of perivascular lymphohistiocytic infiltrate often with dermal mucin noted. Discoid lupus erythematosus (DLE): erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/plugging leading to scarring alopecia on scalp; skin biopsy with typical changes of perivascular and/or periappendageal lymphohistiocytic infiltrate; follicular keratin plugs may be seen in scalp as well as mucin deposition	4
	ACLE	Acute cutaneous lupus (ACLE): malar rash or generalized maculopapular rash; skin biopsy with interface vacuolar dermatitis evidenced by perivascular lymphohistiocytic infiltrate, often with dermal mucin; may have perivascular neutrophilic infiltrate early in course	6
Serosal	Effusion	Imaging (e.g., ultrasound, x-ray, CT, MRI) evidence of pleural or pericardial effusion, or both	5
	Acute pericarditis	$\geq$2 of (1) pericardial chest pain, (2) pericardial rub, (3) EKG with new widespread ST elevation or PR depression, (4) new or worsened pericardial effusion on imaging	6
Musculoskeletal	Joint involvement	Either (1) synovitis involving $\geq$2 joints characterized by swelling or effusion OR (2) tenderness in $\geq$2 joints and $\geq$30 min of morning stiffness	6
Renal	Proteinuria	$>$0.5 g/24 h by 24-h urine or equivalent spot urine protein-to-creatinine ratio	4
	Class II/V	On renal biopsy according to International Society of Nephrology/Renal Pathology Society 2003 classification. II: Mesangial proliferative lupus nephritis; V: Membranous lupus nephritis	8
	Class III/IV	On renal biopsy according to International Society of Nephrology/Renal Pathology Society 2003 classification. III: Focal lupus nephritis; IV: Diffuse lupus nephritis	10
Complements	C3 or C4 low	C3 or C4 below the lower limit of normal	3
	C3 and C4 low	Both C3 and C4 below the lower limits of normal	4
SLE-specific antibodies	Anti-Sm	Anti-Sm antibodies	6
	Anti-dsDNA	Anti-dsDNA antibodies in immunoassay with demonstrated $\geq$90% specificity for SLE against relevant disease controls	6

EKG, electrocardiogram; MRI, magnetic resonance imaging; Anti-Sm, anti-Smith; Anti-dsDNA, anti–double stranded DNA.
Positive ANA is a mandatory criterion; score of $\geq$10 weight points on additive criteria have 96.1% sensitivity and 93.4% specificity for SLE. (Adapted from Aringer M, Costenbader K, Daikh D, et al: European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol 71:1400, 2019.)

validation cohort, these criteria had a sensitivity of 96 percent and specificity of 93 percent for SLE, an improvement over previous classification schemes. Care should be exercised in applying such criteria clinically, particularly for those seronegative for antinuclear antibodies (ANAs).[1]

Patients with SLE present with systemic symptoms including fever, fatigue, and malaise. The most strongly suggestive findings are acute cutaneous (e.g., malar rash or generalized maculopapular rash), musculoskeletal (e.g., synovitis, joint tenderness, and morning stiffness), cardiac (e.g., acute pericarditis), and renal (e.g., nephritis; Table 50-1). Other systemic manifestations include hematologic (e.g., autoimmune hemolytic anemia, leukopenia, thrombocytopenia), neuropsychiatric (e.g., delirium, psychosis, seizure), and serosal. Inflammation can be evident in many tissues and organs, involving not only the heart and kidneys, but also the eyes, lungs, and gastrointestinal tract, among others.[1]

As a systemic autoimmune disease, SLE is characterized by the detection of a variety of autoantibodies. The detection of ANAs at a ratio of at least 1:80 are a mandatory criterion; the threshold is in place since approximately 10 percent of the general population are seropositive at low titers. A minority of SLE patients are seronegative for ANA. Low-level ANA seropositivity has been observed in other inflammatory diseases including connective tissue disorders described later in this chapter such as rheumatoid arthritis, Sjögren syndrome, and systemic sclerosis as well as neurologic diseases such as multiple sclerosis. Other, more specific autoantibodies can be detected in patients with SLE, including anti-Smith (anti-Sm) and antidouble-stranded DNA (anti-dsDNA), which are included in the 2019 EULR/ACR criteria.[1] More than 200 different autoantibodies have been described in SLE, although only a handful are routinely used in clinical practice. Some of these antibodies can occur in subclinical SLE or be predictive very early in the disease course [e.g., anti-Ro60/SSA, anti-Sm, anti-dsDNA, antinuclear ribonucleoprotein (anti-RNP), anti-histone, antiscleroderma 70 kDa antigen (anti-Scl70)], whereas others are pathogenic (e.g., ds-DNA). Of note, some of these antibodies are also detected in other connective tissue disorders (e.g., anti-Ro60/SSA and anti-La/SSB in Sjögren syndrome).

Antiphospholipid antibodies, most commonly those directed to anticardiolipin, are frequently detected in patients with SLE. These antibodies prolong the partial thromboplastin time for patients with SLE and are paradoxically associated with thrombosis more than hemorrhage. Care should be exercised in using anticardiolipin antibodies for diagnostic purposes as they can be detected in those without SLE or other autoimmune diseases, may be detectable only transiently, may be detected in the setting of other systemic illnesses, and may be found in the healthy general population. While 10 percent of healthy blood donors are seropositive for antiphospholipid antibodies, only 1 percent remain seropositive on follow-up testing at 1 year.[2]

Patients with SLE who are seropositive for antiphospholipid antibodies are more likely to develop stroke as well as other neurologic syndromes such as headache, chorea, and myelitis. These patients also are more likely to develop mild cognitive impairment compared to SLE patients who are seronegative for the antibodies. The development of ischemic stroke may be the consequence of the antiphospholipid antibody syndrome, which is characterized by clinical episodes of thrombosis (e.g., deep venous thrombosis, pulmonary embolism, nonbacterial endocarditis, ischemic stroke) or morbid events of pregnancy (e.g., miscarriages typically after 10 weeks gestation, fetal death, pre-eclampsia, eclampsia), especially in the setting of persistence of moderate or high levels of anticardiolipin antibodies. When evaluating patients for concern for antiphospholipid antibody syndrome, additional clinical events or findings should be considered, including a history of arthralgias, livedo reticularis, cardiac valve disease, hemolytic anemia, thrombocytopenia, pulmonary hypertension, acute or chronic renal vascular lesions, and Reynaud phenomenon.[2]

Along with these autoantibodies, complement protein levels are incorporated in the recent clinical criteria, and they play a role in monitoring disease activity. Patients with SLE commonly have levels of complement components C3 and C4 below normal limits, and complement protein levels are particularly low during inflammatory flares.[1] The lowering of circulating levels of these complement proteins is suggestive of immune-complex deposition.

NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

Neuropsychiatric systemic lupus erythematosus (NPSLE) refers to the syndromes of the central, peripheral, and autonomic nervous system as well as the psychiatric syndromes that have been observed in patients with SLE, excluding those syndromes attributable to other causes (Table 50-2).[3] These syndromes can present at any point in the course of SLE, including prior to other systemic manifestations and in those in clinical remission. The reported prevalence of NPSLE and respective syndromes varies widely by study, with estimated prevalence of over 50 percent.[4]

TABLE 50-2 ■ Neuropsychiatric Syndromes in Systemic Lupus Erythematosus

Syndromes	Estimated Prevalence (%)
Central Nervous System Syndromes	
Headache	28.3
Mood disorder	20.7
Cognitive dysfunction	19.7
Seizure	9.9
Cerebrovascular disease	8.0
Anxiety disorder	6.4
Psychosis	4.6
Acute confusional state	3.4
Aseptic meningitis, myelopathy, movement disorder, demyelinating syndromes	Rarely reported, unable to estimate
Peripheral Nervous System Syndromes	
Polyneuropathy	2.3
Cranial neuropathy	2.2
Mononeuropathy (single or multiple)	0.9
Myasthenia gravis, acute inflammatory demyelinating polyradiculopathy (AIDP), autonomic disorder, plexopathy	Rarely reported, unable to estimate

Syndromes as per American College of Rheumatology Ad Hoc Committee on Neuropsychiatric Lupus Syndromes, organized by neurologic category and pooled prevalence from meta-analysis of 17 studies reporting on a total of 5,507 patients with systemic lupus erythematosus.[3,4]

The central neurologic manifestations of NPSLE are widely varied in terms of presentation, severity, mechanisms, and treatment. Seizure, psychosis, and delirium feature in the 2019 EULR/ACR criteria; however, these capture only some of the neurologic syndromes SLE patients may develop as a consequence of SLE and its treatment. Headache, seizure, cognitive dysfunction, and cerebrovascular disease are common central nervous system (CNS) syndromes (Table 50-2).[4]

Headache, in the form of migraine and tension headaches, can occur in patients with SLE; however, it is not clear that these occur more commonly than in the general population. Patients with SLE can develop a new headache syndrome secondary to another etiology, such as posterior reversible encephalopathy syndrome (PRES) in the setting of severe hypertension and some immunosuppressive agents, infection in the setting of chronic immunosuppression, and stroke in the setting of SLE itself.

A minority of patients with SLE have a seizure at some point during the course of their illness, either accompanying one-time events such as metabolic derangements, drug toxicity, or PRES, or in the form of recurrent seizures in the setting of focal brain injury such as stroke.

Cognitive dysfunction is common among patients with SLE, affecting up to one-third of patients. Patients with SLE are nearly three times as likely as healthy individuals to develop cognitive impairment. Such dysfunction is typically mild and rarely severe. Concomitant neuropsychiatric conditions such as mood disorders and stroke can contribute to cognitive dysfunction in SLE.

Psychosis and delirium can develop in patients with SLE from a variety of etiologies, including direct parenchymal inflammation as well as secondary to other systemic processes such as hypertensive encephalopathy and PRES, metabolic derangements, and drug toxicity. Medications commonly used in the acute and chronic treatment of SLE are associated with encephalopathy (e.g., corticosteroid encephalopathy and psychosis), PRES (e.g., cyclosporine, tacrolimus), and opportunistic infections.

An estimated 8 percent of patients with SLE have cerebrovascular disease.[4] Patients with SLE are at increased risk for both ischemic and hemorrhagic stroke, with mechanisms including emboli and thrombosis (usually as a manifestation of antiphospholipid syndrome), atherosclerotic disease, and rarely secondary CNS vasculitis. Given this increased risk, patients with SLE should be treated to address common stroke risk factors for primary stroke prevention. In the event of a stroke, patients should not only undergo brain imaging as part of a secondary stroke prevention assessment, but also a thorough evaluation for vascular stenoses of the head and neck, cardiac evaluation for a cardioembolic source, and evaluation for the presence of antiphospholipid antibodies to characterize risk and individualize treatment.

Other CNS syndromes such as chorea, myelopathy, and aseptic meningitis rarely occur among patients with SLE. Chorea may be unilateral or bilateral, develop slowly at any point through the course of SLE, and resolve spontaneously. Patients often have increased levels of antiphospholipid antibodies. Patients with acute myelopathy as a manifestation of SLE typically present with a syndrome characterized by flaccid, hyporeflexic paraplegia and urinary retention, accompanied by nausea, vomiting, and evidence of active systemic lupus (Fig. 50-1). Their prognosis is poor for neurologic recovery. Patients may also develop a subacute spastic hyperreflexic paraparesis over the course

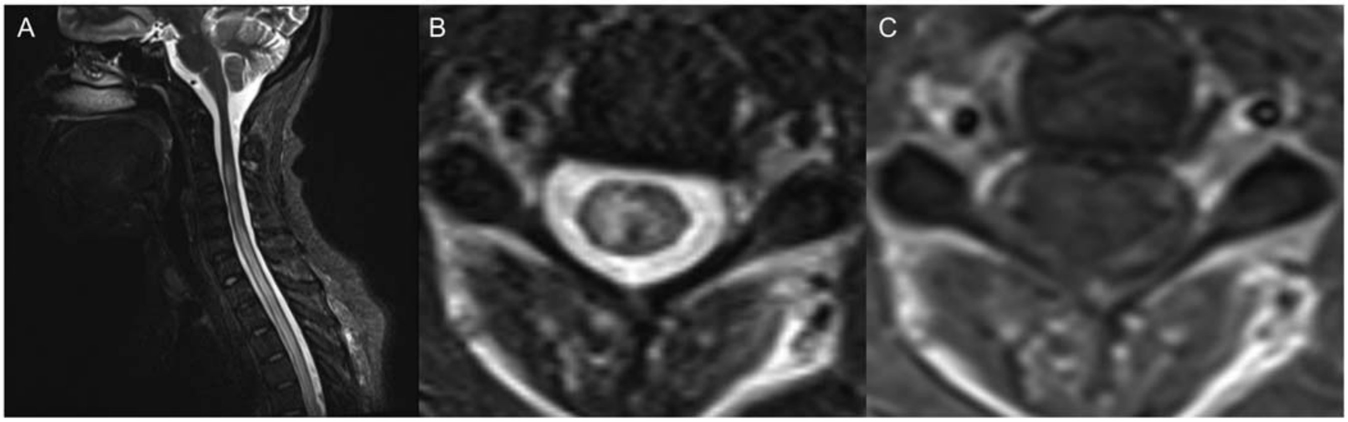

FIGURE 50-1 ■ A patient with systemic lupus erythematosus, seronegative for the aquaporin-4 antibody, presenting with a longitudinally extensive myelitis in the setting of hypocomplementemia. *A*, Magnetic resonance imaging (MRI) of the cervical spine, sagittal STIR sequence, demonstrating patchy T2 hyperintensities beginning at the level of C2–C3 and extending throughout the thoracic cord to the conus (not shown). *B*, Axial T2 sequence demonstrating hyperintensity of the right greater than left gray matter. *C*, Axial T1 postgadolinium imaging did not demonstrate associated enhancement.

of days, typically in the absence of fever or other signs of systemic lupus, which may have a relapsing, remitting course. Patients who present with episodes of myelopathy and optic neuropathy may have a neuromyelitis optica (NMO) spectrum disorder, a minority of whom are aquaporin-4 antibody seropositive.

PERIPHERAL NERVOUS SYSTEM DISEASE

The peripheral nervous system is frequently affected in a variety of connective tissue disorders, including SLE. A minority of SLE patients have evidence of peripheral neuropathies; however, many of these are due to other systemic or noninflammatory causes, such as diabetes or carpal tunnel syndrome, and are therefore not directly attributable to SLE. Sensory predominant or sensorimotor axonal polyneuropathies are the most common manifestations of a symptomatic inflammatory neuropathy due to SLE, affecting 2 to 8 percent of patients (Table 50-2).[4] Mononeuropathy and cranial neuropathy (most commonly of the facial nerve) are rare, while mononeuritis multiplex, acute inflammatory demyelinating polyradiculopathy, and chronic inflammatory polyneuropathy are even rarer (Table 50-2).[4] SLE patients may occasionally develop autonomic neuropathy, sometimes independent of sensory neuropathy, with impairment of sweating, cardiovascular reflexes, and gastrointestinal mobility. Polyneuropathy due to SLE is usually mild, rarely necessitates nerve biopsy, and does not require directed aggressive immunosuppression in addition to the treatment a patient with SLE is already receiving.

TREATMENT

There are a variety of treatments for SLE, with selection guided by the severity of the disease and its impact on affected organs. Aspirin was the first drug approved by the U.S. Food and Drug Administration (FDA) for treatment of SLE, followed by corticosteroids, and later the antimalarial drug hydroxychloroquine. In 2011, belimumab, a monoclonal antibody that blocks the B-lymphocyte stimulator protein, was the first medication specifically approved by the FDA for treatment of SLE. Immunosuppressive medications including cyclophosphamide, methotrexate, azathioprine, and mycophenolate mofetil are also commonly used in the treatment of SLE, particularly in the setting of severe renal or visceral disease.

Symptom-directed therapies play an important role in the treatment of SLE. Just as arthralgias may be treated with nonsteroidal anti-inflammatory drugs, many of the neurologic manifestations of SLE can be managed directly, including headache and mood disorders. Behavioral and cognitive therapy approaches also play an important role in addressing associated cognitive dysfunction.

In addition to symptomatic treatment, syndrome specific treatment is also appropriate in those with neurologic manifestations of SLE. Those with NPSLE presenting with psychosis may be managed with antipsychotic medications as well as steroids (assuming corticosteroid-induced psychosis has been excluded). Catatonia has also been observed in NPSLE and is typically treated with benzodiazepines and rarely with electroconvulsive therapy, in addition to immunosuppressive therapies. Intravenous immunoglobulin (IVIg) and plasmapheresis are mainstays of treating SLE-associated acute inflammatory demyelinating polyradiculopathy. Corticosteroids, plasmapheresis, and immunosuppressive medications such as cyclophosphamide are important considerations for the acute treatment of SLE patients presenting with optic neuritis, focal white matter lesions, and myelitis.

Primary stroke prevention strategies should be employed for patients given the prevalence of stroke among those with SLE. Warfarin is a consideration for those with cardioembolic strokes and the antiphospholipid antibody syndrome, but otherwise antiplatelet medications are the focus of secondary prevention in SLE.

Sjögren Syndrome

SYSTEMIC DISEASE

Sjögren syndrome is another common systemic autoimmune disease, affecting over 1 million American adults. It affects females more than males, with a peak incidence in midlife. It is characterized by an exocrinopathy, commonly manifesting with xerostomia and xerophthalmia, fatigue, and arthralgias, symptoms which are present in over 80 percent of patients. It may be primary, occurring in isolation or along with organ-specific autoimmune diseases such as thyroiditis or primary biliary cirrhosis or secondarily in association with other systemic autoimmune diseases (e.g., SLE, rheumatoid arthritis).[5]

In 2016, the ACR/EULAR jointly released validated classification criteria for Sjögren syndrome. The classification criteria are based on the weighted sums of five items, applied to those patients who have ocular or oral symptoms of dryness or have suspicion for Sjögren syndrome based on one of the domains of the EULAR Sjögren Syndrome Disease Activity Index (Table 50-3). Those patients who have a total score of at least four meet the criteria for Sjögren syndrome. Although designed for purposes of classification, these ACR/EULAR criteria may be useful clinically in the context of common symptoms.[6]

Sjögren syndrome most commonly presents with symptoms of oral and ocular dryness as well as fatigue, symptoms which in and of themselves are common within the general population and may be related to other syndromes including fibromyalgia, medication side effects, aging, and the use of contact lenses. Other constitutional symptoms such as myalgias, weight loss, and fever are reported commonly. Importantly, approximately 30 to 40 percent of patients may present with other systemic manifestations due to involvement of the exocrine glands of not only the eyes and mouth, but also of the skin, lungs, and vagina. Lymphocytic infiltration of epithelia of the kidneys, gall bladder, and lungs may lead to interstitial nephritis, primary biliary cholangitis, and obstructive bronchiolitis, respectively. B-lymphocyte hyperactivity may cause immune complex deposition, resulting in manifestations such as palpable purpura, glomerulonephritis, and interstitial pneumonitis. Thyroid syndromes (thyroiditis, hypothyroidism), gastrointestinal syndromes (atrophic gastritis), and liver disease (biliary cirrhosis) along with organomegaly (spleen and liver) and lymphadenopathy may be observed.[5]

TABLE 50-3 ■ 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification Criteria for Primary Sjögren Syndrome

Domain	Item	Definition	Weighted Points
Serologic assays	Anti-SSA (Ro)	Anti-SSA (Ro) antibody seropositivity	3
Oral tests	Labial salivary gland (LSG) biopsy	LSG biopsy with evidence of focal lymphocytic sialadenitis and focus score ≥ 1	3
	Unstimulated whole saliva (UWS) flow rate	UWS flow rate <0.1 mL/min	1
Ocular tests	Ocular staining score (OSS) or van Bijsterveld score (VBS)	OSS ≥ 5 or VBS ≥ 4 on at least one eye	1
	Schirmer test	Wetting of test strip of <5 mm/5 min by at least one eye	1

Oral and/or ocular symptoms or suspicion for Sjögren syndrome based on domains of the EULAR Disease Activity Index (ESSDAI) are preliminary requirements for application of these classification criteria; score of >4 weighted points on classification criteria with excellent sensitivity and specificity for primary Sjögren syndrome.[6]
Anti-SSA, anti-Sjögren-syndrome-related antigen A.

The pathogenesis of Sjögren syndrome is uncertain. Current models of disease implicate the activation of mucosal epithelial cells, potentially by viruses, leading to an innate and an adaptive immune response, complete with secretion of autoantibodies.[5] These autoantibodies contribute to the formation of immune complexes, leading to immune system activation against, and resultant damage to, affected tissues.[5] In support of this hypothesis, patients with Sjögren syndrome commonly have evidence of systemic autoimmunity, including ANA and anti-SSA/Ro and anti-SSB/La antibodies. The anti-SSA/Ro antibodies are the most specific for Sjögren syndrome.[5,6] Anti-SSB/La seropositivity in the absence of anti-SSA/Ro seropositivity is not specific and thus does not feature in the recent ACR/EULAR criteria.[6] Both anti-SSA/Ro and anti-SSB/La may be detected in patients with other autoimmune diseases, such as SLE. Antibodies not typically seen in Sjögren syndrome can be helpful in distinguishing it from other syndromes, such as anti-dsDNA antibodies, which are included in the classification criteria for SLE.[1] Tissue biopsy and measures of exocrine function are recommended for establishing the diagnosis of Sjögren syndrome.[5]

Providers should be mindful that patients with Sjögren syndrome have an approximate 10 percent lifetime risk for B-cell lymphoma attributed to chronic B-cell activation. These malignancies are primarily B-cell non-Hodgkin lymphomas, often developing in the organs where Sjögren syndrome is primarily active, such as the salivary glands. Thus, it is recommended that every 1 to 2 years, lymphocyte counts and protein electrophoresis along with biomarkers associated with development of lymphoma, namely rheumatoid factor, complement proteins C3 and C4, and cryoglobulins, are assessed.[5]

CENTRAL NERVOUS SYSTEM DISEASE

Approximately 2 percent of patients with Sjögren syndrome develop CNS syndromes. However, this figure is likely an underestimate as many symptoms, such as headache and cognitive dysfunction, may be mild or nonspecific. The most common focal CNS findings in Sjögren syndrome are lesions of the spinal cord. Patients may develop a myelopathy, with various presentations in terms of tempo (rapid vs. slowly evolving), extent of involvement (local vs. more generalized), and presentation (complete transverse myelopathy or Brown-Séquard syndrome). Importantly, as in the case of SLE, Sjögren syndrome patients may also present with longitudinally extensive myelopathies as part of NMO spectrum disorder, often in the setting of aquaporin-4 antibody seropositivity.

In addition to myelopathy, patients with Sjögren syndrome may have demyelinating lesions of the brain parenchyma and optic nerves, with associated clinical syndromes. These may have a relapsing-remitting course, placing Sjögren syndrome as a differential consideration in evaluating patients for possible multiple sclerosis. These radiographic findings are often consistent with those described in NMO, with patients frequently being seropositive for aquaporin 4 antibodies, arguing for their testing in patients presenting with lesions of the CNS.

Syndromes associated with the gray matter, such as seizures, and meningitis are less common. Patients may develop focal brain lesions with associated mononuclear infiltrates of the cerebrovascular system (venous and less commonly arterial) and typically microscopic infarcts of the surrounding brain tissue. Meningeal vessels are also often involved. Patients may present with an aseptic meningitis, with CSF analyses demonstrating a mild mononuclear pleocytosis and elevated protein level. There is rarely detection of unique intrathecal oligoclonal bands or increased immunoglobulin G synthesis relative to the serum in patients with Sjögren syndrome.

PERIPHERAL NERVOUS SYSTEM DISEASE

Peripheral nervous system disease is more common than CNS disease in Sjögren syndrome. Many patients develop neuropathy prior to the diagnosis of Sjögren syndrome, with sicca symptoms preceding or following neuropathic symptoms with equal frequency. The most common of these peripheral nervous system syndromes are sensory neuronopathy and small-fiber neuropathy. Patients less commonly develop trigeminal neuropathy, multiple mononeuropathies, multiple cranial neuropathies, polyradiculoneuropathies, and autonomic neuropathies.

Sensory neuronopathy accounts for nearly 40 percent of all Sjögren syndrome associated neuropathies. It is typically subacute in onset and tempo (occurring over the course of weeks to months) and characterized by multifocal, asymmetric dysfunction of both large and small sensory fibers, manifesting as impaired sensation to proprioception, vibration, temperature, and painful stimuli. Patients may present with pseudoathetosis, as well as symptoms of burning pain, hyperesthesia, and allodynia. Strength usually is preserved but reflexes are diffusely absent. On nerve conduction studies, most patients have absent or low-amplitude sensory nerve action potentials and somatosensory evoked potentials.

MRI of the spinal cord may demonstrate hyperintense signal within the dorsal columns. Important differential considerations for a patient presenting with sensory neuronopathy include other autoimmune syndromes such as SLE, medication or other toxicities (e.g., pyridoxine, cisplatin), infections [e.g., with human immunodeficiency virus (HIV) or varicella zoster virus], hereditary syndromes, and paraneoplastic neuronopathy (e.g., anti-Hu paraneoplastic subacute sensory neuronopathy in the setting of small cell lung cancer). Despite an exhaustive evaluation, half of cases of sensory neuronopathy are idiopathic.[7]

The clinical presentation of a Sjögren syndrome patient with a distal sensory polyneuropathy is typically with a chronic, painful, distal axonal neuropathy involving both small and large sensory fibers. Less commonly, patients present with evidence of distal motor fiber involvement. Autonomic symptoms also are often reported. Nerve biopsy typically demonstrates nonspecific axonal loss, though of variable degree. An idiopathic axonal neuropathy can occur in patients who meet diagnostic criteria for Sjögren syndrome. Conversely, an idiopathic axonal neuropathy, even in the setting of history of dry eyes or mouth, without other objective findings supportive of Sjögren syndrome, does not predict later manifestations of Sjögren syndrome. The key to diagnosis is subsequent serologic testing, ocular and salivary function evaluation, and pathologic tissue review to establish the diagnosis.[7]

Patients presenting with trigeminal neuralgia may present with either unilateral or bilateral numbness or paresthesia restricted to the trigeminal distribution without associated motor symptoms. The syndrome is typically indolent in progression and occasionally accompanied by sensory disturbances in the extremities. Patients may also present with autonomic symptoms including pupillary abnormalities, orthostatic hypotension, and hypohidrosis. Trigeminal involvement can be confirmed by blink reflex testing.[7]

In addition to trigeminal neuralgia, patients may present with other or multiple cranial neuropathies. Patients may present with bilateral nerve involvement including facial diplegia, involvement initially localizable to cranial structures (e.g., oculomotor and trochlear nerve involvement suggesting localization to the cavernous sinus rather than the cranial nerves themselves), and multiple cranial neuropathies which may be misinterpreted as evidence of a meningitis. Involvement of the limbs and trunk is not commonly observed in these syndromes.[7]

Patients may also present with a predominant and severe autonomic neuropathy, with associated symptoms and findings including Adie pupils, orthostatic hypotension, syncope, hypohidrosis or anhidrosis, constipation, and diarrhea.[7]

TREATMENT

Treatment of Sjögren syndrome is directed by the organs involved and the severity of involvement. For oral and ocular dryness, muscarinic agonists such as pilocarpine have shown benefit in randomized clinical trials. Topical cyclosporine eye-drops result in better tear production in comparison to placebo. Otherwise, dry eyes are treated with artificial tears. Regular dental examinations and good oral hygiene are crucial in reducing the risks for dental caries and periodontal disease. For pain management, randomized data are lacking and clinical experience suggests the use of first-line analgesics such as acetaminophen for generalized pain and nonsteroidal anti-inflammatory medications for joint pain. Neuropathic pain is typically treated with serotonin-norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine), and antiepileptics (e.g., gabapentin or pregabalin) with use of tricyclic antidepressants typically limited by the associated side effect of mouth dryness.[5]

No systemic immunomodulatory therapies have been proven efficacious in Sjögren syndrome. In general, extraglandular involvement is treated with systemic immunosuppressive therapies. Commonly used medications are similar to those used for SLE, including azathioprine, cyclosporine, hydroxychloroquine, methotrexate, mycophenolate mofetil, and prednisone. Randomized, controlled trials of the biologic infliximab and etanercept have not demonstrated significant improvement in terms of joint pain, fatigue, and dryness. Small studies of rituximab have yielded mixed results, suggesting its potential utility in the treatment of some systemic manifestations of Sjögren syndrome.[5]

There are no specific treatments for some neurologic accompanying syndromes such as mild cognitive impairment, trigeminal neuropathy, and distal sensory neuropathy. Patients with CNS syndromes including transverse myelitis are typically treated with intravenous corticosteroids as first-line treatment, with plasmapheresis and cyclophosphamide used in refractory cases. Rituximab is indicated for the prevention of subsequent relapses in NMO spectrum disorders. Patients with sensorimotor neuropathy, sensory neuropathy, and small-fiber neuropathy may respond better to IVIg that those with sensory neuronopathy.[7] Patients with mononeuropathies and cranial neuropathies are typically treated with systemic corticosteroids.[7] Accompanying vasculitis or evidence of cryoglobulinemia may predict a response to rituximab. It is advised that treatment plans for neurologic manifestations of Sjögren syndrome be formulated in concert with the patient's rheumatologist.

Systemic Sclerosis

SYSTEMIC DISEASE

Systemic sclerosis (scleroderma) is a multisystem disease characterized by extensive fibrosis, small-vessel vasculopathy, and autoantibody production. Its affects up to 30 persons per 100,000 population, with women more commonly affected than men. Systemic sclerosis varies in presentation and prognosis, with recognized subsets including patients with limited cutaneous systemic sclerosis, diffuse cutaneous systemic sclerosis, and systemic sclerosis without skin involvement.[8] The majority of patients have skin thickening accompanied by involvement of internal organs, most commonly within the limited and diffuse cutaneous subsets. Limited cutaneous systemic sclerosis is mainly restricted to the hands, arms, and face, with Reynaud phenomenon present years before fibrosis is evident; it is typically accompanied by pulmonary hypertension. In contrast, diffuse systemic sclerosis is rapidly progressive, affecting large areas of skin and at least one internal organ. Patients may present with subcutaneous calcinosis, Raynaud phenomenon, esophageal dysfunction (often manifesting as dysphagia), sclerodactyly, and telangiectasia (i.e., CREST syndrome). While some patients may only have CREST, others may have systemic sclerosis manifesting with additional symptoms of pulmonary fibrosis, hypothyroidism, sicca syndrome, renal or cardiac involvement (particularly hypertension), arthralgias, and tenosynovitis. Of note, patients with systemic sclerosis may present with evidence of other concomitant autoimmune syndromes such as SLE, Sjögren syndrome, and rheumatoid arthritis.

The majority of patients have serologic evidence of autoimmunity, including an elevated ANA and antibodies directed against other antigens including centromeres, topoisomerase (Scl-70), RNA-polymerases (to anti-RNA polymerase II), and ribonuclear proteins (U1-RNP and U3-RNP) among other antigens.

In 2013, the ACR/EULAR classification criteria for systemic sclerosis were proposed. Patients may be classified as having systemic scleroderma if there is evidence of skin thickening proximal to the metacarpophalangeal joints. If not present, seven additional items can be used for classification, each of varied weights (Table 50-4). A score of at least 9 on these criteria is associated with good sensitivity and specificity for the diagnosis of systemic sclerosis. It is important to note that these criteria were developed for patient inclusion in studies of systemic sclerosis. These criteria are not applicable to those with finger-sparing skin thickening or a scleroderma-like disorder which may better explain their clinical findings.[8]

CENTRAL NERVOUS SYSTEM DISEASE

CNS involvement in systemic sclerosis is relatively uncommon and it is debatable whether associated neurologic syndromes are the direct result of neurologic injury due to the disease or sequelae of renal, cardiovascular, or pulmonary involvement. Descriptions are largely limited to case reports and series. The most commonly reported CNS syndromes are headache, seizures, and cognitive impairment. Stroke, transverse myelitis, and visual disturbances are described less commonly. Incidental radiographic findings have been reported, most commonly white matter lesions and irregular intracranial vessels, although it is unclear whether these finding represent true pathogenic associations.[9]

PERIPHERAL NERVOUS SYSTEM DISEASE

Peripheral nervous system disease is more common than CNS disease among patients with systemic sclerosis; however, it is difficult to attribute pathogenesis of these syndromes directly to systemic sclerosis. Of the reported peripheral syndromes, myopathy, trigeminal neuropathy, peripheral sensorimotor polyneuropathy, and carpal tunnel syndrome are the most common. Other mononeuropathies and cranial neuropathies have also been described.[9]

Autonomic dysfunction has similarly been reported, typically parasympathetic underactivity and sympathetic overdrive, with prevalence varying across reported case series. At times, autonomic dysfunction can develop prior to evidence of organ fibrosis. The most commonly reported findings include abnormalities of heart rate and blood pressure variability. Gastrointestinal symptoms, esophageal dysfunction, and motility disorders are correlated with autonomic involvement.[9]

TABLE 50-4 ■ 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification Criteria for Systemic Sclerosis (Scleroderma)

Domain	Item	Definition	Weighted Points
Skin and digit findings	Skin thickening of fingers of both hands (Sufficient criterion)	Extending proximal to metacarpophalangeal joints	9
	Skin thickening of fingers (only counting the highest score)	Sclerodactyly of the fingers	4
		Puffy fingers	2
	Fingertip lesions (only counting the highest score)	Fingertip pitting scars	3
		Fingertip ulcers	2
	Telangiectasia		2
	Abnormal nail fold capillaries		2
	Reynaud phenomenon		3
Pulmonary findings (max. 2 points)	Pulmonary arterial hypertensions	Pulmonary arterial hypertension	2
	and/or Interstitial lung disease	Interstitial lung disease	2
Serologic assays (max. 3 points)	Anticentromere		1
	Antitopoisomerase I		1
	Anti-RNA polymerase III		1

Designed for purposes of study inclusion, apply care in clinical application. These criteria are not applicable to those patients with skin thickening sparing the fingers nor to those with a scleroderma-like disorder which better explains their manifestations. The total score is determined by adding the maximum weight score in each item category. A score of >9 weighted points on classification criteria has good sensitivity and specificity for systemic sclerosis.[8]

TREATMENT

Treatment of systemic sclerosis centers on the management of related organ complications. Data on the treatment of neurologic syndromes in patients with systemic sclerosis are limited to case reports and series, with therapy largely focused on the neurologic disorder (e.g., antiepileptic medications for seizures, surgery for entrapment neuropathies). Many disorders are not treated specifically, such as mild neuropathies.

Rheumatoid Arthritis

SYSTEMIC DISEASE

Rheumatoid arthritis (RA) is multisystem disorder characterized by chronic destructive synovitis. It is the most common rheumatologic disease in adults, affecting over 1 million Americans, with increasing prevalence among those older than 65 years. The pathogenesis of rheumatoid arthritis is uncertain, although it is characterized by activation of endothelial cells leading to synovial membrane infiltration by B and T lymphocytes and monocytes, as well as neovascularization. The consequent expanded synovial membrane ("pannus") invades periarticular bone, leading to bony erosions and cartilage degradation. A variety of molecules have been identified which mediate the signs and symptoms of RA as well as the degradation of bone and cartilage; these molecules have emerged as targets of therapy, including tumor necrosis factor and interleukin-6. The majority of patients with RA have positive autoimmune serologies, most commonly rheumatoid factor which itself is nonspecific and detectable in a small percentage of the normal population. Anticitrullinated protein antibodies are more specific for the diagnosis of rheumatoid arthritis.

Early in the disease course, RA may manifest with involvement of only one or a few joints. Tenosynovitis may also develop at the same time or even earlier. Over time, patients develop the characteristic symmetric, polyarticular disease. Patients typically present with pain and synovitis of the joints of the hands and feet, accompanied by morning joint stiffness of at least 30 minutes to hours. If insufficiently treated, patients may develop extra-articular disease. Extra-articular disease occurs in over half of patients, manifesting as subcutaneous rheumatoid nodules (most common), sicca syndrome, Felty syndrome (RA, neutropenia, and hypersplenism), amyloidosis, scleritis or episcleritis, lung or heart involvement, anemia of chronic disease, eosinophilia, thrombocytosis, and rarely systemic vasculitis. RA vasculitis is necrotizing, involving small or medium-sized arteries, typically of the skin but occasionally of other organs, including those of the nervous system. Thus, patients with RA are at risk for other comorbidities due to chronic inflammation. Cardiovascular disease is common and the primary cause of death in RA; it is associated with RA disease activity. Patients may also develop interstitial lung disease, either as a manifestation of RA or as a complication of its treatment.

In 2010, the ACR and EULAR revised the 1987 ACR classification criteria to address concerns for sensitivity in the setting of early disease. The new criteria require the confirmed presence of synovitis in at least one joint, the absence of an alternative diagnosis for the synovitis, and a score of at least 6 of a possible 10 points across four domains: number and site of joints involved, serologies, evidence of an acute-phase response, and symptom duration (Table 50-5).[10]

Central Nervous System Disease

Syndromes involving the CNS are less frequent than those of the peripheral nervous system. The CNS manifestations can be nonfocal such as headache or focal including optic neuropathy and compressive myelopathy. Patients rarely develop focal cerebral disease. In chronic RA, stroke due to rheumatoid vasculitis is rare, as are meningitis and meningoencephalitis.

Cervical spine disease is a common late complication of RA and includes bony erosions and pannus compression, as well as atlanto-axial, subaxial, and vertical subluxation. In the setting of chronic inflammation, inflamed ligaments become lax and allow for subluxation, which is typically anterior but can occur in all directions. The subluxation is usually asymptomatic; however, risk for cord compression increases with increased subluxation. Over time, patients may develop progressive signs of compressive myelopathy such as quadriparesis, spasticity, and sphincter dysfunction that may evolve slowly or worsen suddenly. Patients with vertical atlanto-axial subluxation can develop signs not only of cervical myelopathy but also brainstem compression, including ophthalmoparesis, nystagmus, trigeminal or high cervical sensory loss, bulbar palsy, hydrocephalus, sleep apnea, and drop attacks. Rarely, patients with neck subluxation present with vertebral artery stroke.

Symptomatic management of atlanto-axial subluxation can entail cervical collars to decrease neck pain or headache, as well as halo devices and cervical traction for neck stabilization. Patients with compressive myelopathy with and without brainstem compression should undergo surgical stabilization as they are at risk for subluxation progression and further neurologic morbidity. Surgical stabilization does not tend to improve existing neurologic deficits, but rather halts their progression.

Patients with RA may develop neuropsychiatric syndromes including depression, anxiety, and cognitive impairment. When evaluating a patient with RA presenting with such syndromes, corticosteroid encephalopathy and associated mood disturbance is an important differential consideration in addition to infectious sequelae of chronic immunosuppression.

Rarely, patients may develop rheumatoid meningitis or meningoencephalitis. Clinical presentations vary, with nonspecific symptomatology including headache and cognitive dysfunction as well as focal neurologic deficits and seizures. MRI with gadolinium may demonstrate thickening and enhancement of the pachymeninges and leptomeninges as well as rheumatoid nodules that may be mistaken for malignancy. Cerebrospinal fluid analyses may be normal or demonstrate a monocytic pleocytosis with elevated protein. Given concern for malignancy as well as opportunistic infection in the setting of chronic immunosuppression, brain and meningeal biopsy may be pursued and demonstrates mononuclear cell infiltrates, necrosis, and occasionally granulomas. In addition, patients may develop a meningitis or meningoencephalitis in the setting of tumor necrosis factor-α inhibitor treatment itself. They may also develop normal-pressure hydrocephalus as a consequence of chronic meningeal inflammation.

Just as patients with RA are at increased risk for cardiovascular disease, they are similarly at risk for cerebrovascular disease. RA-associated cardiovascular syndromes, including congestive heart failure and valvular disease, place patients at increased risk of stroke, warranting careful primary stroke prevention evaluation. Rheumatoid vasculitis involving the cerebral arteries occurs rarely, but can manifest as stroke and stroke-like syndromes.[11]

Peripheral Nervous System Disease

Patients with RA may develop various compressive mononeuropathies, including at the ulnar groove, carpal tunnel, and tarsal tunnel. Patients may also develop neuropathies of the digits or of the fibular or posterior

TABLE 50-5 ■ 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis (RA)

Domain	Item	Definition	Score
Entry criterion	At least 1 joint with synovitis that is not better explained by another disease	Synovitis refers to swelling	
Joint involvement	1 large joint	"Large joints" includes shoulders, elbows, hips, knees	0
	2–10 large joints	Defined as per above	1
	1–3 small joints	"Small joints" include metacarpophalangeal, proximal interphalangeal, second through fifth metatarsophalangeal, thumb interphalangeal, and wrists; with or without large joint involvement	2
	4–10 small joints	Defined as per above; with or without large joint involvement	3
	>10 joints	Must include at least one small joint, all other joints may be any combination of large and small joints as defined above as well as other joints (e.g., temporomandibular, acromioclavicular, sternoclavicular)	5
Serologies (at least 1 test result is needed for classification)	Negative RF *and* negative ACPA	RF refers to rheumatoid factor; ACPA refers to anticitrullinated protein antibody; International Unit (IU) values are less than or equal to upper limited of normal (ULN) for respective laboratory or assay	0
	Low-positive RF *or* low-positive ACPA	Low-positive is defined as higher than ULN but ≤3 times the ULN for the respective laboratory or assay	2
	High-positive RF *or* high-positive ACPA	High-positive is defined as >3 times the ULN for the respective laboratory or assay	3
Acute-phase reactants (at least 1 test result is needed for classification)	Normal C-reactive protein (CRP) *and* normal erythrocyte sedimentation rate (ESR)	Normal as per local laboratory standards	0
	Abnormal CRP *or* abnormal ESR	CRP and ESR defined as per above; abnormal as per local laboratory standards	1
Duration of symptoms	<6 weeks	Duration of symptoms of less than 6 weeks per patient self-reported synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at time of assessment regardless of treatment status	0
	≥6 weeks	6 weeks or more of patient self-reported duration of symptoms in joints that are clinically involved at time of assessment regardless of treatment status	1

Classification criteria were developed for newly presenting patients, but are applicable to those patients with erosive disease typical of RA and a compatible history as well as those with longstanding disease. Criteria should be applied to those patients with at least one joint with definite clinical synovitis (swelling), with the synovitis not better explained by another disease (e.g., SLE, psoriatic arthritis, gout). Classification of definite RA is achieved with a total score of 6 or greater (of a possible 10) weighted points from individual scores in the four domains.[10]

tibial nerves. These mononeuropathies may be the result of compression by subcutaneous rheumatoid nodules, severe joint disease, a popliteal Baker cyst, or from synovial inflammation and thickening. The most common neurologic manifestation of RA is carpal tunnel syndrome. Successful treatment of RA together with carpal tunnel surgery (occasionally with tenosynovectomy) may improve carpal tunnel syndrome symptoms. Treatment of mononeuropathy is otherwise focused on management of RA and associated inflammation.

A length-dependent symmetric sensorimotor neuropathy is a potential late effect of RA, particularly in those with severe disease. The neuropathy is typically mild. When performed, nerve biopsy may demonstrate vasculitic changes; however, these changes are not an indication for systemic immunosuppressive therapy. Patients may also develop an autonomic neuropathy, manifesting with impaired sweating and abnormal postural and cardiovascular reflexes, which may develop in the absence of sensory neuropathy. Patients may also develop mononeuritis multiplex in the setting of rheumatoid vasculitis.[12]

Patients with RA may develop inflammatory myositis in a variety of forms including dermatomyositis (DM), polymyositis (PM), and vasculitic myositis. A noninflammatory myopathy sometimes arises in the setting of disuse as well as from chronic corticosteroid administration.

TREATMENT

RA is incurable, with recommended treatment goals being remission or low disease activity through the use of disease-modifying antirheumatic drugs (DMARDs). It is important to note that pain medications and nonsteroidal anti-inflammatory medications may improve symptoms, but they do not prevent the progression of disease toward irreversible disability. DMARD treatments include synthetic, small orally administered molecules (e.g., methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, and the janus kinase inhibitors) as well as biologics (e.g., parenterally administered proteins such as etanercept, infliximab, adalimumab, and rituximab). A treat-to-target strategy is recommended, with the aim of reducing disease activity and achieving remission within 6 months. Methotrexate and corticosteroids feature in the initial management, together leading to low disease activity and remission in almost half of patients with early RA. In the setting of failure of response to initial therapy, additional synthetic DMARDs or biologics are introduced. In the setting of remission, dose reduction rather than cessation of all DMARDs is recommended.

Myopathies in Connective Tissue Disease

Inflammatory myopathies are a heterogeneous group of potentially treatable disorders, classified based on distinct clinical and pathologic features. The classic subtypes of inflammatory myopathies include DM, PM, inclusion-body myositis (IBM), and necrotizing autoimmune myositis (NAM). In addition, antisynthetase syndrome and overlap myositis syndromes are increasingly recognized.

Patients typically present with symmetric, subacute proximal weakness with difficulty in daily activities such as rising from seated to standing, ascending stairs, and lifting objects above the head. Ocular muscles are spared, and while facial and distal muscles may be involved early in IBM, distal muscle involvement typically occurs late in DM, PM, and NAM. Across these subtypes, serum creatine kinase is typically markedly elevated, up to 50 times the upper limit of normal in DM, PM, and NAM and up to 10 times normal in IBM. Electromyography (EMG) demonstrates myopathic changes including easily recruited, brief, low-amplitude motor unit action potentials (with mixed large-amplitude potentials in IBM) along with fibrillation potentials and positive sharp waves. Despite similarities, these syndromes can be distinguished based on distinct clinical, histopathologic, and pathophysiologic features.[13,14]

Myositis overlap syndromes are characterized by an autoimmune myopathy (typically DM or PM) occurring in the setting of a connective tissue disease such as SLE, Sjögren syndrome, systemic sclerosis, or rheumatoid arthritis. At the time of presentation with myositis, serologic evidence (but not necessarily clinical features) of connective tissue disease is present in up to 15 percent of patients. A minority of patients with SLE have evidence of inflammatory myopathy based on muscle enzyme elevation, but asymptomatic SLE patients may have evidence of muscle inflammation on biopsy.

DM can rarely occur in those with systemic sclerosis and mixed connective tissue disorder.[13] DM can affect children and adults, and typically manifests with both skin and muscle involvement. The proximal muscles are typically involved, accompanied by neck flexor, pharyngeal, or diaphragmatic weakness in those with more severe disease. Pathognomonic skin manifestations of DM include scaly, erythematous lesions of the extensor surfaces of the joints of the hand (Grotton nodules) and discoloration of the eyelids occasionally accompanied by periorbital edema (heliotrope rash). Patients may also have an erythematous rash of the upper arms and shoulders (shawl sign) as well as subcutaneous calcium nodules. In addition to skin and muscular manifestations, 20 to 30 percent of patients have interstitial lung disease, particularly in those seropositive for antibodies to aminoacyl-tRNA synthetases (anti-Jo) and melanoma differentiation-associated protein 5 (MDA5).[14] The hallmark histologic features of biopsied muscle include perifasicular atrophy of myocytes as well as perimysial and perivascular inflammation. DM may also occur as a paraneoplastic syndrome in association with hematologic and lymphatic cancers or various adenocarcinomas, breast cancer, and melanoma.[13,14]

PM is a rare myopathy, often misdiagnosed in those with other inflammatory muscle disorders (including IBM and NAM), and thus PM is a diagnosis of exclusion.[13,14] It is a myopathy of adults which is subacute in onset and progression, sparing extraocular and facial muscles, and occurring in the absence of rash, family history of neuromuscular disease, or toxic exposures.[13] EMG demonstrates active myopathic units while MRI may show areas of active muscle inflammation which may guide muscle biopsy.[13] Inflammatory infiltrates of muscle fibers, typically composed of $CD8^+$ lymphocytes, are seen histologically in biopsied muscle.[13,14]

Antisynthetase antibodies are detected in approximately one-quarter of patients with overlap myositis. This antisynthetase syndrome is characterized not only by myositis but also arthritis, fevers, hyperkeratotic lesions of the radial and palmar surfaces (mechanics hands), interstitial lung disease, and Raynaud phenomenon. Some patients may also have erythematous rashes similar to that of DM. Patients with antisynthetase syndrome were previously classified as having either DM or PM based on the presence or absence of such rash. However, histopathologic findings of perifascicular necrosis and sarcolemmal complement deposition suggest antisynthetase syndrome is distinct from DM and PM.[14]

When evaluating a patient with connective tissue disease for potential myopathy, it is important to be mindful of the potential myopathic side effects of immunosuppressant medications. Corticosteroids, particularly in the setting of chronic or high-dose courses, can induce a type-II muscle fiber atrophy, presenting with mild proximal weakness in the setting of normal serum creatine kinase and a noninformative EMG. Long-term, high-dose use of chloroquine can also cause a myopathy, characterized by weakness in the setting of a normal serum creatine kinase level. Cyclosporine and tacrolimus rarely cause a myopathy. Penicillamine can induce both PM and DM, both of which improve with its cessation.

VASCULITIS

The vasculitides are disorders characterized by blood vessel inflammation. They can be categorized by type and size of inflamed blood vessels, location in the body, and pathologic features. The majority are systemic, with isolated neurologic involvement rarely occurring. Primary CNS vasculitis (PCNSV) and nonsystemic vasculitic neuropathy (NSVN) are the classic primary vasculitides of the nervous system.

Primary Vasculitides of the Nervous System

PRIMARY VASCULITIS OF THE CENTRAL NERVOUS SYSTEM

PCNSV is an uncommon, poorly understood varied group of disorders collectively characterized by idiopathic, predominantly monocytic, transmural inflammation of the vascular wall of small and medium-sized vessels of the brain parenchyma, spinal parenchyma, and leptomeninges. Historically, PCNSV has been referred to as granulomatous angiitis or primary angiitis of the nervous system. The pathogenesis of PCNSV is uncertain, with one hypothesis that it is a secondary inflammatory syndrome following a primary infection, such as varicella zoster virus. A rare and potentially treatable disease, PCNSV affects both children and adults; however, it most frequently presents in men at a median of 50 years of age.[11]

Clinically, patients present with an insidious and slowly progressive course, although some presentations may be acute. Syndromes vary, with nonspecific manifestations being most common, such as headache and subacute encephalopathy. In contrast to systemic vasculitis, fever and other systemic symptoms are uncommon. Patients frequently present with persistent motor, sensory, and language deficits, often in the setting of seizures. Ischemic, and less commonly hemorrhagic, stroke is common.

Serum blood tests are typically normal in patients with PCNSV, with occasional nonspecific elevations in the acute-phase reactants erythrocyte sedimentation rate (ESR) and C-reactive peptide (CRP), and detection of ANA and antiphospholipid antibodies. Levels of the von Wildenbrand factor antigen are often elevated in children with PCNSV, particularly those with small-vessel involvement.

The neurologic evaluation can be suggestive but not diagnostic of PCNSV. CSF analyses commonly demonstrate a mild pleocytosis and elevated total protein concentration. Electroencephalogram is most often nonspecific, with generalized or focal slowing commonly reported. MRI with gadolinium can show evidence of both cortical and subcortical infarction (most commonly multiple and bilateral), intracranial hemorrhage, parenchymal and leptomeningeal enhancement, and possibly mass-like lesions. MR angiography, however, is of limited utility, particularly for the evaluation of vessels of the posterior circulation as well as small, distal blood vessels. This emphasizes the importance of CT-based or conventional angiography in demonstrating findings suggestive of vasculitis, including alternating segments of vascular stenosis and dilatation, arterial occlusions, and rarely microaneurysms in multiple, bilateral, large and small blood vessels.[11]

The gold standard for diagnosis remains neurosurgical biopsy of the dura, leptomeninges, cortex, and white matter, ideally with radiographic guidance targeting involved areas rather than random sampling. When performed by a skilled neurosurgeon, the risk for neurologic complication is as low as 1 percent. Importantly, biopsy allows for the demonstration of vasculitis as well as the evaluation for mimics. Long-term immunosuppressive treatment can decrease the sensitivity of biopsy, emphasizing the importance of aggressively pursuing diagnosis in suspected cases.[11]

There are three main types of PCNSV, each with distinct pathologic features without evolution, suggesting that these are distinct types rather than different stages of the same disease. The most common is granulomatous, characterized by angiocentric mononuclear inflammation, granulomas, and multinucleated giant cells. β-Amyloid deposition in vessel walls is demonstrated in half of patients with granulomatous PCNSV. Lymphocytic PCNSV occurs in approximately one-quarter of patients, more commonly in children with angiography-negative PCNSV, and it is characterized by a predominant lymphocytic inflammation with occasional plasma cells and vessel wall destruction. The third and least common is necrotizing PCNSV, which is characterized by transmural fibrinoid necrosis; it is associated with intracranial hemorrhage. Occasionally, necrotizing and granulomatous findings are noted together.[11]

Several clinical criteria and subsequent refinements have been proposed for the diagnosis of PCNSV. The most widely used clinical criteria require a history and findings of an acquired neurologic deficit of unknown etiology; characteristic angiography findings (e.g., alternating areas of smooth-wall narrowing and dilation of arteries, occlusions of cerebral blood vessels, absence of proximal vessel involvement, and absence of findings suggestive of alternative etiologies); biopsy demonstrating histopathologic evidence of vasculitis; and no evidence of systemic vasculitis or other attributable etiology. Some reserve a definitive diagnosis of definite vasculitis for those patients with vasculitis proven by biopsy review, while those with angiographic evidence of a primary cerebral vasculitis and supportive brain MRI and CSF findings without available biopsy tissue are classified as having probable PCNSV.[11]

It is important to be mindful of the syndromes that may mimic PCNSV. CNS vasculitis can be secondary to systemic infections (e.g., varicella, HIV, syphilis, aspergillosis, cystercercosis, bacterial endocarditis, bacterial meningitis), systemic vasculitides [e.g., antineutrophil cytoplasmic antibodies (ANCA)–associated vasculitides, Behçet disease], connective tissue diseases (e.g., SLE, RA, Sjögren syndrome), antiphospholipid syndrome, lymphoma, neurosarcoidosis, and drugs such as stimulants. It is important to distinguish patients with PCNSV from those with reversible vasoconstrictive syndrome (RCVS) and other noninflammatory vasculopathies. RCVS typically affects women in the postpartum period or after exposure to vasoconstrictive agents. In contrast to PCNSV, subarachnoid hemorrhage is a common presentation while ischemic and hemorrhagic stroke are less commonly observed in RCVS.[11]

With no randomized controlled treatment trials, treatment of PCNSV is guided by the experience of reported cases, cohort studies, and expert opinion. Treatment typically entails an induction phase with corticosteroids alone or along with cyclophosphamide, and maintenance therapy with mycophenolate mofetil, azathioprine, or methotrexate. The vast majority of patients have a favorable response to various combinations of induction therapy, but up to one-third of treated patients experience relapse.

Nonsystemic Vasculitic Neuropathy

NSVN presents most commonly as a slowly progressive, asymmetric, multifocal neuropathy. Also referred to as primary vasculitis of the peripheral nervous system, it usually affects patients in their seventh decade of life, more commonly women. It rarely presents acutely. The clinical course is typically insidious with a long duration of symptoms prior to diagnosis. In contrast to neuropathies associated with the systemic vasculitides discussed later in this chapter, symptoms are confined to the peripheral nervous system. Weight loss is reported in roughly one-third of patients, while fever is reported in a minority of patients. The most common neurologic presentations are of either multiple mononeuropathy, asymmetric polyneuropathy, or distal symmetric polyneuropathy affecting both motor and sensory nerves. Pain is a frequent symptom. NSVN has a low rate of morbidity and even lower rate of mortality. Patients commonly experience chronic pain; however, they are typically independent in mobility and activities of daily living. Patients with NSVN should be followed longitudinally as approximately 10 percent of patients will later be found to have a systemic vasculitis.[12]

As NSVN is a diagnosis of exclusion, the diagnostic approach to a patient presenting with a painful, asymmetric, multifocal neuropathy is to assure it is not due to a systemic vasculitis. Blood tests including complete blood cell counts, chemistry panels, glucose levels and glycated hemoglobin, acute-phase reactants, serum protein electrophoresis, complement levels, cryoglobulins with hepatitis serologies, and serologic testing for systemic vasculitides are performed to evaluate for not only systemic vasculitis, but also infections, hematologic malignancy, and metabolic mimics. Patients with NSVN may have nonspecific abnormalities on testing, such as elevated ESR, peripheral leukocytosis, thrombocytosis, and elevated ANA. Serologies for connective tissue disorders such as SLE, infections such as with HIV and spirochetes, and radioimaging such as plain chest radiograph or CT (for sarcoid) may be performed based on the clinical history and examination.[12]

EMG and nerve conduction studies are central to the diagnosis. They frequently demonstrate evidence of acute to subacute patchy, multifocal, nonlength-dependent axonal sensorimotor neuropathy, either mononeuropathy or, more commonly, polyneuropathy. Additionally, there may be evidence of conduction block at the nidus of nerve infarction.[12]

Electrodiagnostic testing is also important in guiding muscle and nerve biopsy. Inflammatory infiltration and occasionally necrosis of the epineurial and perineurial large arterioles are seen in NSVN. Inflammation of the small arterioles, capillaries, and venules may also be seen in the setting of microvasculitis. The inflammatory infiltrates are typically associated with immune complex, complement, and fibrinogen deposition in the epineurial blood vessel walls; neovascularization; and multifocal fiber loss with perineurial thickening and Wallerian degeneration of nerve fibers. Although patients may have no clinical evidence of myopathy, muscle biopsy may demonstrate vasculitis within muscle tissue, particularly of the perimesial arterioles.[12]

Corticosteroids are the cornerstone of treatment of NSVN. Patients with a history of clinical progression and histopathologic evidence of active NSVN should be treated with high-dose oral prednisone or prednisolone (typically 1 mg/kg per day) followed by a long slow taper over the course of months. Less often, patients may have evidence of active vasculitis on biopsy but be clinically improving; treatment or observation with close clinical follow-up may be considered. In severe cases, high-dose intravenous methylprednisolone followed by a slow oral corticosteroid taper may be pursued. If patients demonstrate progression despite corticosteroids, cyclophosphamide can be used as second-line therapy, preferably intravenously in severe cases. After stabilization, some patients may be transitioned to azathioprine or methotrexate for maintenance therapy.[12]

Systemic Vasculitis

SYSTEMIC DISEASE

The noninfectious, systemic vasculitides can be broadly categorized by the size of the affected vessels, which differ in their structure and function. Large-vessel vasculitides (i.e., giant-cell arteritis and Takayasu arteritis) will be discussed separately later in this chapter. Vasculitides of the medium vessels (medium arteries to arterioles) and small vessels (small arteries, arterioles, capillaries, venules, and small veins) can also affect both the central and peripheral nervous system and are discussed here. These conditions include the medium-vessel arteritis polyarteritis nodosa (PAN) and the ANCA-associated small-vessel vasculitides granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg—Strauss syndrome), and microscopic polyangiitis (MPA). Kawasaki disease, a medium-vessel vasculitis, primarily occurs in children and rarely manifests with neurologic syndromes.[15]

PAN is a rare systemic vasculitis, affecting the main medium-sized visceral arteries as well as their small artery and arteriole branches. It can be a sequela of chronic hepatitis B virus infection, with increased incidence in areas where hepatitis B is endemic. It most commonly affects men, typically between 40 and 50 years of age. PAN presents with constitutional symptoms including fever, malaise, fatigue, and weight loss, with the majority of patients demonstrating skin involvement (e.g., livedo reticularis, cutaneous nodules, skin ulcerations, ischemia of the digits), Patients also commonly have joint and kidney involvement, including hypertension, renal artery aneurysms, and renal infarction. Less commonly, patients manifest with testicular involvement, cardiac involvement (e.g., tachycardia, patchy myocardial ischemia and infarction, heart failure), and rarely pulmonary or otolaryngologic involvement. Gastrointestinal manifestations are common, with patients often presenting with abdominal pain, frequently in the setting of microaneuryms of the mesentery. The most common neurologic manifestation of PAN is neuropathy, affecting the majority of patients and most commonly in the form of multiple mononeuropathies. Cranial nerve and CNS involvement rarely occur.[12]

Through the course of diagnostic evaluation, patients with PAN are found to be seronegative for ANCA and are often found to have evidence of systemic inflammation including elevated ESR, leukocytosis, thrombocytosis, and anemia.[12] Renal function may be impaired, as evidenced by elevated blood urea nitrogen and creatinine, with proteinuria and hematuria found on urine analysis. Biopsies of affected organs demonstrate necrotizing arteritis of small and medium arteries; no involvement of the arterioles, capillaries, or venules; and no evidence of glomerulonephritis on renal biopsy.[15]

GPA is an ANCA-associated vasculitis of the small and medium vessels, which initially manifests with involvement of the respiratory tract before involving other organs over the course of months. It is characterized by necrotizing granulomatous inflammation of small arteries, arterioles, capillaries, venules, and small veins.[15] It most commonly manifests with involvement of the upper airway with ulcerations of pharynx and ears; lower airway including ulcerations of lungs, transient infiltrates, or even pulmonary hemorrhage; and kidney with glomerulonephritis.[12] Less commonly it affects the muscles and joints, eyes, skin, and rarely the heart (e.g., pericarditis) and gastrointestinal tract (up to 10%).[12] Up to 25 percent of patients have involvement of the peripheral nervous system, while up to 10 percent show involvement of the CNS, and 15 percent have cranial neuropathies.[12]

On laboratory testing, up to 90 percent of GPA patients are seropositive for ANCAs [more often with antiproteinase 3 (PR3) than antimyeloperoxidase (MPO) antibodies], while 25 percent are ANA seropositive.[12] Patients commonly demonstrate evidence of systemic inflammation, with elevated ESR, leukocytosis, thrombocytosis, and anemia commonly noted.[12] Classification of GPA by the ACR is based on the presence of at least two of the following: nasal or oral inflammation, abnormal chest radiograph, microhematuria or red cell casts in the urine, or pathologic demonstration of granulomatous inflammation involving organ arteries or arterioles.

EGPA is less common than GPA and MPA. It is characterized by necrotizing granulomatous inflammation rich in eosinophils affecting small and medium blood vessels.[15] In contrast to PAN, patients with EGPA have eosinophilia in the setting of pulmonary involvement, primarily asthma and pulmonary infiltrates, which are evident in up to 75 percent of patients.[12] Patients also commonly present with rhinosinusitis and involvement of the skin, gastrointestinal tract, joints, heart, and kidney.[12] Up to 70 percent of patients develop neuropathy, with CNS (10 to 15%) and cranial neuropathies (less than 5%) being less common.[12] Patients initially develop asthma and allergic rhinosinusitis followed by eosinophilia in the peripheral blood and eosinophilic pneumonia, followed years later by evidence of systemic vasculitis.[12] The ACR classification of EGPA is based on the presence of four of the following: asthma, eosinophilia, mononeuropathy or polyneuropathy, transient pulmonary infiltrates, abnormal paranasal sinuses, and nasal polyps.

On laboratory assessment, all EGPA patients have eosinophilia, with ESR commonly elevated. Patients may have elevated immunoglobulin E levels. Only 30 to 40 percent are ANCA seropositive, more commonly anti-MPO than anti-PR3. ANCA seropositivity is associated with renal disease, particularly in those with necrotizing glomerulonephritis, which otherwise is not common in EGPA.[12]

MPA is another common ANCA-associated vasculitis. It is characterized by a nongranulomatous necrotizing vasculitis with a paucity of immune deposits involving small vessels; inflammation is isolated to these vessels.[12] In contrast to PAN, necrotizing glomerulonephritis and pulmonary capillaritis are common.[15] Patients are predominantly male, with an average age between 60 and 70 years. The majority present with constitutional symptoms. The most common systemic manifestations involve the kidney, joints, skin, lungs, gastrointestinal tract, and less commonly the ears, nose, throat, and heart.[12] Peripheral neuropathies are observed in 45 percent of patients, while the CNS is involved in 10 to 15 percent.[12] On laboratory testing, patients are frequently seropositive for ANCA (75 to 85%), more commonly anti-MPO than anti-PR3, and have an elevated ESR.[12] In contrast to PAN, patients with MPA do not have evidence of hepatitis infection.[12] Patients with MPA do not meet criteria for either GPA or EGPA.[12]

Importantly, vasculitis can be a manifestation of a variety of diseases, including connective tissue disorders and infections. Rheumatoid vasculitis affects medium-sized vessels, and is typically a late manifestation of severe RA. Patients may develop neuropathy along with other evidence of systemic vasculitis. Sjögren syndrome is associated with a microvasculitis, typically of epineurial vessels, without other systemic involvement. Vasculitis can also occur in SLE and sarcoidosis. Infectious vasculitides are an important consideration. While hepatitis B is associated with PAN, chronic hepatitis C with cryoglobulinemia causes a medium-vessel vasculitis itself, leading to a vasculitic neuropathy. Similarly, HIV is associated with a medium-vessel vasculitis, thought to be due to immune complex deposition.[18] HIV vasculitis occurs in less than 1 percent of infected individuals, typically in the setting of CD4 counts less than 500 cells/µL. Vasculitides can also occur due to viral (e.g., cytomegalovirus, varicella zoster virus), bacterial (e.g., borrelia, syphilis, ricketsial, mycobacterial), and fungal (e.g., histoplasma, cryptococcal) infections. Medium-vessel vasculitides can rarely be paraneoplastic, presenting as a painful sensorimotor neuropathy or mononeuritis. The most commonly associated cancers are small cell lung cancer and lymphoma, and the most commonly reported associated antibody is to antineuronal antigen–1 (anti-Hu).[12]

CENTRAL NERVOUS SYSTEM DISEASE

CNS vasculitis in the context of systemic vasculitis can present as a variety of syndromes in patients of all ages. In the setting of constitutional symptoms, patients may develop syndromes ranging from the seemingly benign (e.g., headache) or nonspecific (e.g., concentration problems, encephalopathy) to focal and localizable (e.g., seizures, stroke, meningitis). Of note, ischemic strokes can occur in single or multiple locations, typically in small-vessel areas. As noted earlier, the frequency of CNS involvement varies across the small- and medium-vessel systemic vasculitides, most frequently in ANCA-associated vasculitides.[12]

PERIPHERAL NERVOUS SYSTEM DISEASE

Vasculitis of the medium and small vessels can manifest as a systemic vasculitic neuropathy, which typically presents with an acute-to-subacute, painful, sensory or sensorimotor neuropathic syndrome in the setting of constitutional symptoms such as fever, fatigue, weight loss, night sweats, and, in some instances, a skin rash. Classically, patients present with an ischemic mononeuropathy or mononeuritis multiplex characterized initially by deep, aching pain of the proximal limb, followed in short order by burning dyasthesias or parathesias and focal weakness in the distribution of a single nerve, followed subsequently by involvement of additional discrete nerves over the course of weeks. In time, the overlap of mononeuropathies can present clinically as an asymmetric or even symmetric polyneuropathy. Approximately one-third of patients present with a slowly progressive, distal, symmetric sensorimotor neuropathy. The majority of patients with EGPA and PAN present with a peripheral neuropathy, while those with GPA and MPA are less likely to have neuropathy as a presenting symptom. Cranial nerves may be involved (potentially multiple, particularly in GPA). Rarely, patients present with a syndrome of acute ascending paralysis, with electrodiagnostic studies demonstrating an axonal rather than demyelinating polyradiculopathy and evidence of vasculitis on nerve biopsy. The pathologic findings of systemic vasculitic neuropathy on muscle and nerve biopsy are similar to those described previously for NSVN. MPA may manifest with inflammation of small blood vessels, while GPA may lead to epineurial granulomas and EGPA with granulomas accompanied by eosinophilic infiltration.[12]

TREATMENT

The treatment of systemic vasculitis is two part: induction therapy followed by maintenance therapy over the course of months to years. Corticosteroids (prednisone or methylprednisolone) and cyclophosphamide (either intravenous or oral) are standard induction therapies commonly given in combination for moderate to severe PAN, GPA, EGPA, and MPA. Remission is typically achieved over the course of months of corticosteroid tapering and cyclophosphamide therapy, and patients may be transitioned to azathioprine or methotrexate as maintenance therapy. Cyclosporine, leflunomide, and mycophenolate mofetil are common second-line maintenance therapies.[12]

Polymyalgia Rheumatica and Giant-Cell Arteritis

SYSTEMIC DISEASE

GCA, also referred to as "temporal arteritis," is the most common primary large-vessel arteritis, affecting adults 50 years or older and often associated with polymyalgia rheumatica (PMR).[16] PMR is the more common syndrome, affecting up to 10 times the number of patients as GCA.[16] Both typically affect the elderly, with peak incidence in the eighth decade and a female predominance.[16] GCA is characterized pathologically by granulomatous arteritis with giant cells involving the aorta and its major branches.[15] The carotid branches, vertebral arteries, and temporal arteries are commonly affected.

PMR is a chronic, idiopathic systemic inflammatory illness characterized by aching pain and stiffness, particularly upon waking in the morning. The aching pain is distributed symmetrically and involves the proximal joints, particularly the shoulders more so than the neck or pelvis. Imaging studies of patients with PMR demonstrate inflammation of the joints, including bursas and periarticular structures. Muscle weakness does not feature in the syndrome; however, myalgias are a key feature and are accompanied by elevated acute serum phase reactants. Patients commonly manifest systemic symptoms of fever, malaise, fatigue, anorexia, and weight loss.[16]

Approximately half of patients with GCA initially present with PMR.[16] Systemic symptoms such as fever, fatigue, and weight loss are characteristically accompanied in GCA by headache and jaw claudication. Patients may report or be demonstrated on examination to have scalp pain and enlarged, nodular arteries of the scalp, particularly the temporal arteries. Having a high index of suspicion for GCA is particularly important given the risk of luminal occlusion and associated ischemic complications such as ischemic optic neuropathy and stroke.[16] Among those with GCA, approximately 20 percent have aortitis and are at risk for aortic dissection, aortic aneurysms, and associated syndromes such as aortic valve insufficiency, myocardial infarction, and intestinal ischemia.[16] Less than 10 percent of patients have inflammation of the subclavian-axillary and brachial arteries, and approximately 5 percent demonstrate inflammation of the superficial femoral and popliteal arteritis.[12] Involvement of these vessels leads to asymmetric pulses, Raynaud phenomenon, and symptoms of claudication in the extremities. Glomerulonephritis occurs in approximately 10 percent of patients.[12] The most common neurologic syndromes are otologic (60 to 90% of patients) or involve the optic nerve (15 to 20%).[12] Rarely, the peripheral and central nervous systems are involved.[12]

The most common laboratory abnormalities of both PMR and GCA are an elevated ESR and CRP. Patients are also commonly anemic and demonstrate thrombocytosis and leukocytosis. Approximately 30 percent of patients have abnormal liver function studies. ANCAs are rarely detected, and their detection is suggestive of an ANCA-associated vasculitis rather than GCA.[16]

When GCA is suspected, biopsy of the temporal artery should be pursued to confirm the diagnosis. GCA is characterized by patchy vascular inflammation, and therefore biopsy should be ideally performed on vessels that are abnormal on palpation. Biopsy is diagnostic in 85 to 95 percent of cases; however, if a first biopsy is histologically normal, biopsy of the contralateral temporal artery should be pursued. Importantly, treatment with corticosteroids should not be deferred out of concern for affecting biopsy yield. Following tissue confirmation of GCA, magnetic resonance angiography or computed tomographic angiography can be used to evaluate the aorta and its major branches to assess the extent of GCA involvement.[16]

Central Nervous System Disease

Headache is a common presenting symptom and typical of GCA. New-onset headache in a patient older than 50 years of age should raise concern for GCA, particularly in the setting of other typical symptoms such as PMR, fever, jaw claudication, and unexplained weight loss.[16]

Arteritic ischemic optic neuropathy occurs in up to 20 percent of patients with GCA.[12] It can lead to irreversible vision loss. Patients typically experience sudden, painless, monocular vision loss that progresses over the course of days. The vision loss may occasionally be of the entire visual field in the affected eye, the consequence of central retinal artery occlusion. It may be proceeded by amaurosis fugax, a syndrome of brief, transient episodes of painless vision loss. Patients less commonly report retrobulbar pain. On examination, there is typically loss of light perception and an afferent pupillary defect once infarction has occurred. Funduscopic examination at 24 to 48 hours after symptom onset demonstrates optic disc swelling and pallor as well as occasional flame-shaped hemorrhages or cotton wool spots. High-dose intravenous corticosteroids should be initiated promptly in suspected cases while the confirmatory diagnostic evaluation, including temporal artery biopsy, is pursued.[16]

Other CNS syndromes, such as stroke and transient ischemic attack (TIA), rarely occur in patients with GCA. When they do occur, strokes are typically embolic, with a predilection for the posterior cerebrovascular circulation (since the vertebral arteries are commonly inflamed) more than the anterior circulation. Intracranial arteries are rarely involved.

Peripheral Nervous System Disease

Otologic syndromes due to cranial nerve ischemia are common in GCA. Approximately 90 percent of patients are affected by vestibular dysfunction and 60 percent experience hearing loss. Patients may also have other ischemic cranial neuropathies, including the oculomotor nerve, or ischemia of the extraocular muscles themselves. Peripheral neuropathies, both focal and multifocal, rarely occur. The cervical nerve roots, upper brachial plexus, and distal median nerve (often due to carpal tunnel syndrome) are most commonly affected.[12]

Treatment

Corticosteroids are the standard treatment for both GCA and PMR. The initial treatment of GCA is prednisone at a dose of 1 mg/kg per day for 2 to 4 weeks followed by a slow taper. Monitoring of ESR and CRP allows for assessment of response to therapy and guides the prednisone taper. New-onset symptoms, such as arteritic ischemic optic neuropathy, are treated with intravenous methylprednisolone, typically at a dose of 1,000 mg daily for 3 days followed by a slow oral prednisone taper. Aspirin should be considered in patients with GCA given the associated stroke risk.[16]

In contrast, PMR is treated with lower doses of prednisone (typically 15 to 20 mg daily initially) over the course of several months, with monitoring for remission of symptoms. Prednisone taper is typically at a rate of 20 percent or less each month, and is again guided by acute-phase reactant levels and clinical monitoring.[16] Unfortunately, corticosteroid-sparing agents such as methotrexate are of either marginal or no benefit in GCA.[16]

Takayasu Arteritis

SYSTEMIC DISEASE

Originally described in Japan, Takayasu arteritis is the most common arteritis among those of Asian ancestry. Commonly referred to as "pulseless disease," it is an idiopathic vasculitis of the large vessels, including the aorta, major arterial branches, and the pulmonary artery. Histopathologically, it is characterized by granulomatous inflammation of the large arteries. Similar to GCA both clinically and histopathologically, age of onset in patients less than 50 years of age is a key distinguishing feature of Takayasu arteritis.[15]

Clinically, patients initially present with systemic symptoms of fever, malaise, weight loss, anorexia, nausea, and vomiting. On examination, patients frequently demonstrate findings of erythema nodusum and synovitis. Systemic inflammatory symptoms and signs precede vascular involvement. In time, patients develop vascular stenoses and occlusions, impairing blood flow in the large vessels, particularly of the extremities; this leads to difficult in palpating peripheral pulses and to limb claudication and arterial bruits. Patients may have hypertension secondary to renal artery stenosis, and additional findings including Reynaud phenomenon, tenderness of the involved arteries, or aortic valve insufficiency as a consequence of aortic root inflammation.

Paraclinical findings include elevated levels of acute-phase reactants such as ESR and CRP, as well as other signs of inflammation including peripheral leukocytosis and anemia.[12] These laboratory findings and systemic symptoms may resolve spontaneously, leaving only arterial stenoses and occlusions as the findings characteristic of Takayasu arteritis. In this setting, arteriography can be used to assess the extent of disease involvement of the aorta and its major vessels, including the carotid and vertebral arteries. Takayasu arteritis usually does not affect the peripheral nervous system.

CENTRAL NERVOUS SYSTEM DISEASE

Inflammation of the carotid and vertebral arteries puts patients at risk for ischemic stroke as well as TIA. Patients are also at risk for embolic stroke in the setting of myocardial infarction from coronary artery inflammation. Takayasu arteritis does not involve the intracranial arteries. Ischemic stroke risk is driven by carotid and vertebral artery stenoses and hypertension. This hypertension, which is a risk factor for intracranial hemorrhage, is often caused by renal artery stenosis.

TREATMENT

As with GCA, corticosteroids are the standard treatment of Takayasu arteritis. Despite corticosteroid therapy, many do not improve and relapses are common. Vascular complications occur in the majority of patients. Patients may require vascular surgical bypass, stenting, or angioplasty of arterial stenoses; however, these stenoses often recur despite intervention.

Behçet Disease

SYSTEMIC DISEASE

Behçet disease is an idiopathic vasculitis with variable involvement of vessels of all sizes.[15] Patients present with a history of acute episodes of recurrent oral aphthous ulcers, recurrent genital aphthous ulcers, eye lesions (uveitis, retinal vasculitis, or both), and a variety of cutaneous lesions including erythema nodosum, pseudofolliculitis, papulopustular lesions, and acneiform nodules in postadolescent patients.[17] These features along with a positive pathergy test feature in the diagnostic criteria.[17] Less frequently, patients experience episodes of arthritis, epididymitis, gastrointestinal inflammation and ulceration, vascular complications (e.g., arterial occlusions, aneurysms, thrombophlebitis), and inflammatory lesions of the CNS.[17]

Behçet disease varies in prevalence between populations, although cases cluster along the ancient Silk Road from Japan to the eastern Mediterranean. Globally, the prevalence is approximately 10 per 100,000 population, with the highest prevalence in Turkey. Behçet disease is more common among males than females; however the ratio of male-to-female patients varies across studied cohorts. Patients typically develop symptoms when 20 to 30 years of age.[17]

There are no specific paraclinical findings for Behçet disease. Patients often have elevated markers of systemic inflammation. Sensitivity and specificity of the skin pathergy test vary across populations.[17]

CENTRAL NERVOUS SYSTEM DISEASE

Approximately 10 to 15 percent of patients with Behçet disease develop neurologic syndromes, though this varies across populations. Patients develop neurologic symptoms between 20 and 40 years of age, and men are more frequently affected neurologically than women.

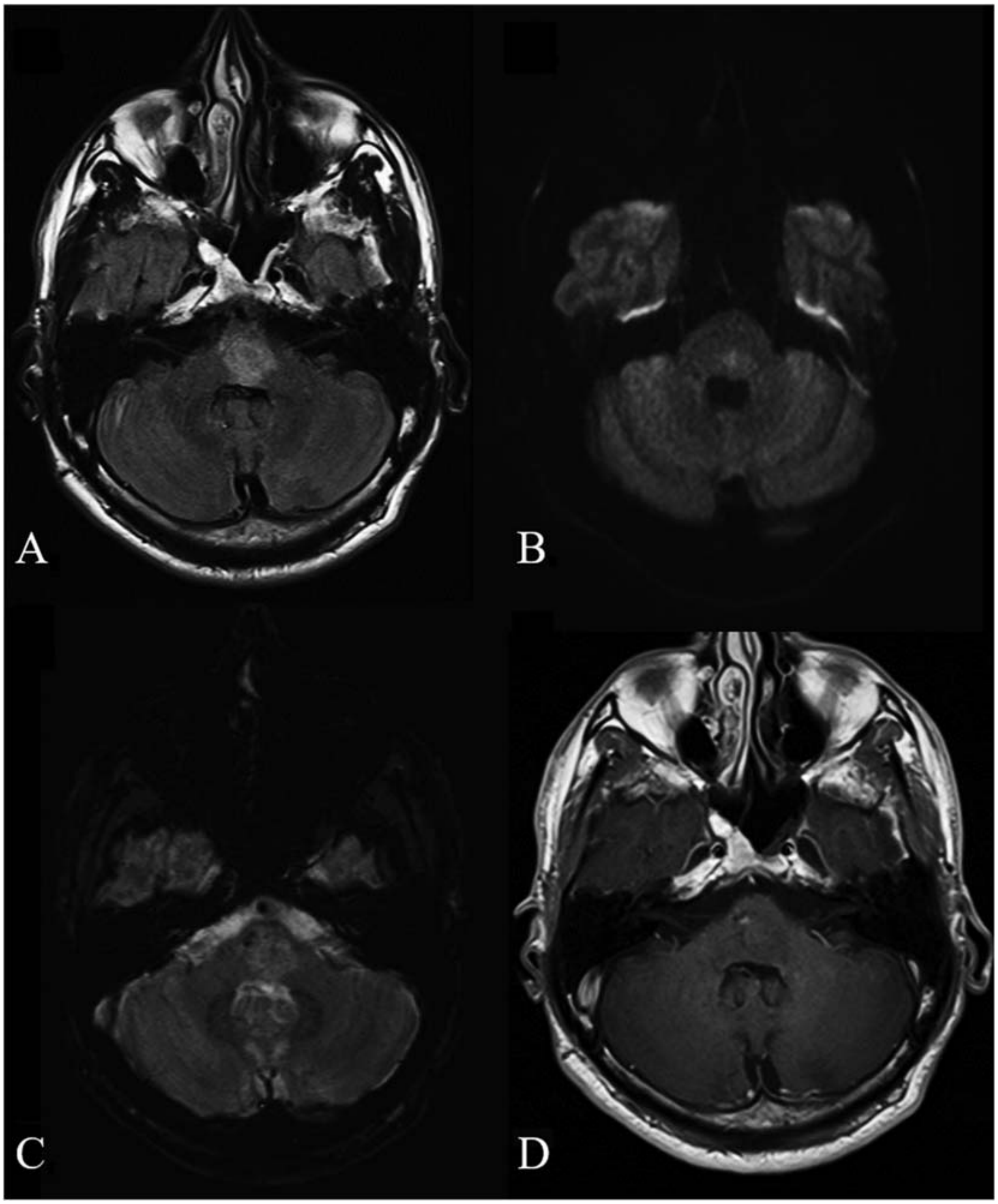

FIGURE 50-2 ■ Parenchymal neuro-Behçet disease. *A*, MRI brain fluid-attenuated inversion recovery sequence demonstrates a heterogeneous T2 hyperintensity within the pons extending to the left cerebellar peduncle. *B*, Diffusion-weighted sequence demonstrates mild diffusion restriction within the lesion. *C*, Susceptibility-weighted sequence demonstrates hypointensities in the right pons compatible with hemosiderin deposition. *D*, Postgadolinium T1 sequence demonstrates mild enhancement within the pons near the areas of hemosiderin deposition.

Neurologic manifestations typically arise 3 to 6 years after the onset of other systemic features of Behçet, primarily involving the CNS.[17]

Neurologic Behçet disease is divided into two groups: a parenchymal group with meningoencephalitis predominantly affecting the brainstem, and a nonparenchymal group with thrombosis within the dural venous sinuses. In the acute phase, parenchymal disease is characterized by a small-vessel perivascular inflammatory infiltrates composed of neutrophils, eosinophils, basophils, lymphocytes, and monocytes with areas of apoptotic neuronal loss and necrosis. This inflammation can involve the brainstem, subcortical gray matter, and white matter (Fig. 50-2). Parenchymal involvement is the most common manifestation of neurologic Behçet disease. Of those with parenchymal disease, approximately 75 percent present with a subacute meningoencephalitis, with fever, malaise, and headache occurring both before and during an attack. The symptoms of meningoencephalitis develop over the course of days and persist for weeks. Patients with parenchymal involvement can also develop a variety of syndromes based on areas of inflammation, including cranial neuropathies (e.g., optic neuropathy), ophthalmoparesis, cerebellar dysfunction, extrapyramidal and pyramidal dysfunction, stroke-like syndromes, seizures, cognitive syndromes, psychosis, and spinal cord involvement (e.g., transverse myelitis). Rarely, imaging studies may demonstrate lesions that mimic tumors.[17]

Nonparenchymal Behçet disease is less common, accounting for 20 percent of cases of neurologic disease. Stroke is rare in neurologic Behçet disease in general, and is typically caused by nonparenchymal disease. Central venous sinus thrombosis (CVST) is a common nonparenchymal syndrome, and is typically subacute to chronic in onset. Patients may develop intracranial hypertension in the presence as well as in the absence of CVST. Patients with CVST may also rarely develop seizures. Intracranial aneurysms have been occasionally reported in the setting of Behçet disease, but these are likely coincidental rather than the consequence of the syndrome.[17]

Disease activity has been associated with elevations in ESR, and thrombocytosis may be noted, particularly in those with CVST. Up to 80 percent of patients with parenchymal disease have abnormal CSF profiles, typically featuring a modest elevation in CSF protein in the setting of a neutrophilic-predominant pleocytosis which transitions to a lymphocytic-predominant pleocytosis in the chronic phase of disease. MRI may demonstrate T2 hyperintensities of the involved parenchyma, and these abnormalities typically enhance and are associated with edema (Fig. 50-2). Atrophy may be evident in the setting of chronic disease. MRI of the spinal cord in patients with a transverse myelitis typically demonstrates lesions that mimic demyelinating plaques, some of which are longitudinally extensive. Venography (either MR or CT) readily demonstrate thromboses.[17]

PERIPHERAL NERVOUS SYSTEM DISEASE

Cases of peripheral neuropathy, mononeuritis multiplex, myopathy, and myositis have been reported in patients with Behçet disease; however, the relation of these reported syndromes to Behçet disease is uncertain.[17]

TREATMENT

There are no controlled or comparative treatment trials for Behçet disease, with choice of therapy directed by individual clinical manifestations. For parenchymal disease, a course of high-dose intravenous methylprednisolone followed by a slow oral prednisone taper is used; abrupt cessation is avoided given concern for early relapse. The role of other forms of immunosuppression in neurologic Behçet disease is uncertain. CVST may be treated by anticoagulation with heparin or low-molecular-weight heparin as well as corticosteroid therapy.[17]

Patients with acute parenchymal lesions recover well after steroid treatment; however, some patients recover without treatment. Approximately one-third of patients have a progressive disease course, with accrual of neurologic deficits in the setting of recurrent episodes.[17]

ACKNOWLEDGMENT

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SECTION

12

Sleep and Its Disorders

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CHAPTER 51

Neurologic Aspects of Sleep Medicine

RENEE MONDERER ■ SHELBY HARRIS ■ MICHAEL THORPY

SLEEP PHYSIOLOGY
- Sleep Stages
  - *Stage Wake*
  - *Stage N1*
  - *Stage N2*
  - *Stage N3*
  - *Stage REM*
- Sleep Patterns Across the Human Lifespan

CIRCADIAN NEUROBIOLOGY

NEUROANATOMY OF SLEEP

APPROACH TO THE PATIENT WITH SLEEP DISORDERS
- Clinical Evaluation
- Laboratory Testing
  - *Polysomnography*
  - *Multiple Sleep Latency Test*
  - *Maintenance of Wakefulness Test*
  - *Actigraphy*
  - *Home Sleep Studies*

INSOMNIA
- Standardized Definitions
- Risk Factors and Common Comorbidities
- Consequences
- Clinical Assessment and Diagnosis
- Pathophysiology
- Treatment
  - *Cognitive Behavioral Therapy*
  - *Pharmacologic Interventions*

HYPERSOMNIAS
- Narcolepsy
  - *Clinical Features*
  - *Diagnosis*
  - *Pharmacologic Treatments*
  - *Nonpharmacologic Treatments*
- Idiopathic Hypersomnia
- Kleine–Levin Syndrome

SLEEP-RELATED BREATHING DISORDERS
- Epidemiology
- Definitions
- Symptoms
- Predisposing Factors
- Physiologic Consequences
- Clinical Evaluation
- Treatment
  - *Positive Airway Pressure Therapy*
  - *Surgery*
  - *Upper Airway Stimulation*
  - *Oral Appliances*
  - *Behavioral Modifications*

CIRCADIAN RHYTHM DISORDERS
- Delayed Sleep Phase Disorder
- Advanced Sleep Phase Disorder
- Shift Work Disorder
- Jet Lag Disorder
- Irregular Sleep–Wake Disorder
- Non–24-Hour Sleep–Wake Rhythm Disorder

SLEEP-RELATED MOVEMENT DISORDERS
- Restless Legs Syndrome
- Periodic Limb Movements

PARASOMNIAS
- NREM Parasomnias
  - *Sleepwalking (Somnambulism)*
  - *Confusional Arousals*
  - *Sleep Terrors*
  - *Treatment of Arousal Disorders*
- REM Parasomnias
  - *Nightmares*
  - *REM Sleep Behavior Disorder*
- Other Parasomnias
  - *Sleep-Related Eating Disorder*
  - *Sexsomnia*
  - *Forensic Implications*
  - *Exploding Head Syndrome*

SLEEP DISORDERS IN PATIENTS WITH NEUROLOGIC DISORDERS
- Parkinson Disease
- Alzheimer Disease
- Epilepsy
- Stroke
- Headache

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Sleep disorders commonly occur in patients who present to neurologists. At times, symptoms are obvious, such as insomnia or excessive daytime sleepiness (EDS). However, some patients have serious sleep disorders, such as sleep apnea, that are often not readily apparent to the patient or physician and can exacerbate a neurologic disorder. Established links exist between sleep apnea and stroke, epilepsy, and migraine, between certain sleep behavior disorders and neurodegenerative diseases, and between circadian rhythm disorders and dementia. In light of these links, it is important that neurologists become familiar with sleep disorders and incorporate sleep diagnosis and treatment into daily practice, and that sleep specialists and internists gain wider appreciation of the impact of sleep disorders on neurologic function and disease. This chapter reviews key aspects of sleep medicine and their association with clinical neurology.

SLEEP PHYSIOLOGY

Sleep is defined by behavioral and physiologic changes that include postural recumbence, behavioral quiescence, eye closure, and specific physiologic parameters based on electroencephalography (EEG), electro-oculography (EOG), and electromyography (EMG). Sleep is further subdivided into non—rapid eye movement (NREM) and rapid eye movement (REM) sleep.

The normal adult brain enters sleep first through NREM stages followed by REM sleep approximately 90 minutes later. NREM and REM sleep then alternate through four to six cycles lasting 90 to 110 minutes each. The first third of sleep is dominated by NREM sleep and the last third of the night is dominated by REM sleep. NREM sleep is further divided into three stages (N1, N2, N3).

Sleep Stages

The staging of sleep is based on the recordings of the EEG, chin EMG, and EOG made during polysomnography (PSG). The PSG is scored by assigning a sleep stage to each 30-second epoch recorded. The characteristics of the various sleep stages are summarized in Fig. 51-1.

STAGE WAKE

Stage wake can occur when the subject is alert with eyes open or relaxed with eyes closed. When the eyes are open, the EEG shows low-amplitude, fast mixed-frequency activity. The EOG tracing consists of eye movements and eye blinks, and the EMG chin activity is increased. Once the eyes are closed, alpha rhythms (8 to 13 Hz) predominate on the EEG and are most prominent in the occipital leads. This alpha activity attenuates with concentration or with eye opening. Stage W is scored when 50 percent of the epoch shows alpha activity in the occipital region. The normal adult spends less than 5 percent of the night in this stage.

STAGE N1

Stage N1 sleep is characterized by light sleep or drowsiness. It is identified by less than 50 percent of the epoch being occupied by alpha activity on the EEG. The EEG also shows low-voltage, mixed-frequency activity predominantly in the theta frequency (4 to 7 Hz). The EOG channel often shows slow rolling eye movements, and EMG activity is diminished. Vertex sharp waves may appear in the central EEG leads in the later part of stage N1. In the normal adult, stage N1 should occupy 2 to 5 percent of sleep, but patients with excessive sleep fragmentation such as those with sleep apnea often have a larger percentage of stage N1 sleep.

STAGE N2

Stage N2 sleep is defined by the presence of K-complexes or sleep spindles on the EEG. The background EEG shows low-amplitude, mixed-frequency activity. The EOG typically shows no eye movements, but slow rolling eye movements may persist from stage N1. EMG activity is reduced from stage N1 and wake. Stage N2 generally constitutes 45 to 55 percent of sleep in adults.

STAGE N3

Stage N3 sleep, also referred to as slow-wave sleep, represents the deepest sleep stage. Slow-wave sleep was initially divided into stages 3 and 4; however, because of the physiologic similarities between these stages, they have been combined into a single stage. Stage N3 is defined by the presence of high-amplitude slow waves with a frequency of 0.5 to 2 Hz and an amplitude of 75 μV. Slow-wave activity must occupy at least 20 percent of the epoch to meet criteria for stage N3. The EMG is active but diminished compared to stages W and N1, and there are no eye movements. Stage N3 occupies 15 to 25 percent of sleep in healthy adults.

STAGE REM

REM sleep is characterized by a highly active brain with loss of muscle tone. The EEG shows a low-voltage, mixed-frequency pattern with sawtooth waves. The chin EMG

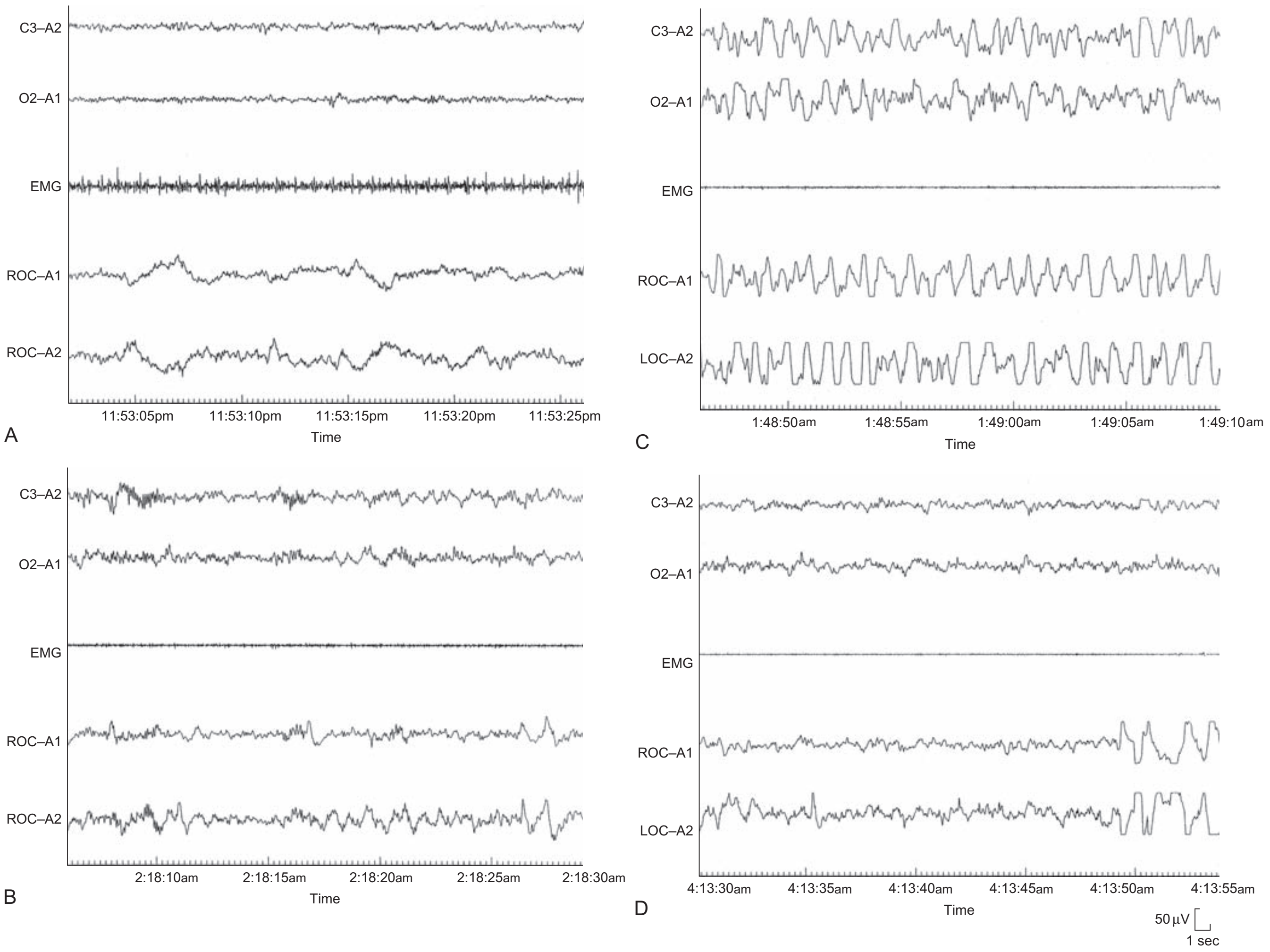


FIGURE 51-1 ■ The stages of sleep. *A*, Stage N1. There is low-voltage mixed-frequency electrocerebral activity with ongoing muscle activity and slow, rolling eye movements. *B*, Stage N2 sleep showing sleep spindles. K-complexes are also classically present but are not clearly shown in this epoch. *C*, Stage N3 sleep, with high-amplitude, low-frequency delta activity in the electroencephalogram (EEG). The eye-movement channels reflect the EEG. *D*, Stage REM. The EEG is of low amplitude and mixed frequency and is accompanied by muscle atonia and rapid eye movements. (Adapted from Abad VC, Guilleminault C: Polysomnographic evaluation of sleep disorders. p. 727. In Aminoff MJ (ed): Aminoff's Electrodiagnosis in Clinical Neurology. 6th Ed. Elsevier Saunders, Oxford, 2012.)

tone is markedly diminished, and the EOG shows rapid eye movements. There is a cessation of K complexes, sleep spindles, and high-amplitude waves. REM sleep accounts for 20 to 25 percent of total sleep time in healthy adults.

Sleep Patterns Across the Human Lifespan

Sleep patterns change markedly throughout the human lifespan. The most pronounced changes occur during the first year of life. Newborns enter sleep through REM sleep (called "active sleep" in the newborn), and then sleep alternates between REM and NREM in 50- to 60-minute intervals rather than the 90-minute cycles of adults. During the first year of life, EEG patterns develop to allow distinction between different stages of NREM sleep.

Stage N3 sleep is most prominent in childhood and decreases by almost 40 percent in the second decade of life. It further declines with age and is almost absent by the age of 60, especially in men, perhaps due to a decline in the amplitude of EEG waves from reduced synaptic activity.

REM sleep occupies 50 percent of sleep in the first year of life. By 6 years of age, REM sleep time is reduced to 20 to 25 percent of sleep and is maintained at this percentage into old age. REM sleep markedly declines with organic brain dysfunction.

Arousals and episodes of awakening from sleep increase dramatically with age and may correlate with an underlying sleep disorder, medical condition, or neurologic disease. The percentage of stage N1 sleep also increases with age, signifying more transitions between wake and sleep.

Sleep requirements change with age. A newborn sleeps about 16 hours per day. This falls to about 11 hours in children 3 to 5 years of age. Adolescents between 9 and 10 years of age require approximately 10 hours of sleep. Adults average 7.5 to 8 hours of sleep; although this duration remains steady into healthy old age, the ability to consolidate sleep into a single continuous sleep period declines. Elderly individuals may revert to a biphasic sleep pattern with increased daytime napping.

CIRCADIAN NEUROBIOLOGY

The sleep–wake cycle is regulated by two opposing processes, the circadian rhythm and the homeostatic drive for sleep. The circadian rhythm is set by the suprachiasmatic nucleus of the hypothalamus, which regulates the sleep–wake cycle. The suprachiasmatic nucleus projects to the pineal gland to release melatonin, which promotes sleep. The nucleus is synchronized by external cues known as *zeitgebers*, of which the strongest is light. Light inhibits the release of melatonin from the pineal gland and in this way sleep is influenced by the day–night cycle.

The homeostatic process refers to an increased propensity for sleepiness with longer periods of being awake. Adenosine is a byproduct of the waking brain, and levels rise with prolonged periods of wake, increasing the tendency for sleep. Caffeine is an adenosine antagonist and is used to promote wakefulness.

In the morning, the suprachiasmatic nucleus output is low. The homeostatic drive increases over the day and is opposed by increased output from the suprachiasmatic nucleus. By the end of the day, suprachiasmatic nucleus output is decreased through inhibition by melatonin, and the homeostatic drive is increased, resulting in the onset of sleep.

The circadian rhythm of sleep becomes clinically relevant when the sleep–wake cycle is changed such as in shift work or jet lag. Adaptation becomes difficult both because of sleep loss and increased homeostatic drive for sleep and because the circadian rhythm continues on its own established schedule. Elderly individuals who have difficulty consolidating sleep and those with neurodegenerative diseases often have disruption of the normal cycling of sleep consistent with circadian rhythm disorders. Light therapy can be a useful tool to help reset the circadian rhythm and establish a normal sleep–wake cycle.

NEUROANATOMY OF SLEEP

Changes between wake, NREM, and REM sleep are produced through modulation of neurotransmitters and neuromodulators interconnecting the neuronal system that regulates sleep.

The ascending arousal system is important in maintaining wakefulness. It is composed of a cholinergic branch and a monoaminergic branch. The cholinergic branch includes the pedunculopontine and laterodorsal tegmental nuclei, which project to the thalamic reticular nucleus in order to activate the cerebral cortex. Acetylcholine excites the thalamic and cortical neurons maximally during wake and REM sleep.

The monoaminergic branch includes the locus coeruleus, dorsal and median raphe nuclei, tuberomammillary nuclei, and ventral periaqueductal gray matter. Histamine (H_3), norepinephrine, and serotonin are released from these various nuclei, which are also maximally active during wakefulness in order to activate the cerebral cortex. The monoaminergic system is quiet in NREM sleep and turned off in REM sleep. Hypocretin neurons in the lateral hypothalamus augment this activation of the cortex during wakefulness.

Dopamine is elevated during periods of wakefulness, and dopaminergic neurons modulate cortical activation indirectly through regulatory activity of the globus pallidus and the thalamus.

Sleep onset is associated with a rapid deactivation of both the monoaminergic and cholinergic branches of the arousal system. GABAergic neurons in the preoptic hypothalamus promote sleep onset. The ventrolateral preoptic nucleus sends descending inhibitory projections to multiple arousal systems during sleep.

The homeostatic process and the circadian clock determine the activity of the ventrolateral preoptic nucleus. In NREM sleep, this nucleus inhibits both the cholinergic and monoaminergic branches of the ascending arousal system to induce sleep. In REM sleep, only the monoaminergic nuclei are inhibited, but the cholinergic nuclei are active.

REM sleep is driven by cholinergic neurons in the pons. Descending cholinergic projections produce muscle atonia by activating neurons in the pontine reticular formation and ventral reticular formation that then project to the spinal cord. Glycine is the essential neurotransmitter in these pathways.

The monoaminergic nuclei also inhibit the ascending arousal system during wakefulness, resulting in a system of reciprocal inhibition. This has been termed the "sleep switch." Both sides of the switch strongly inhibit each other, resulting in a feedback loop with only two possible states: sleep and wakefulness.

Hypocretin is the stabilizer of this switch. In wakefulness, hypocretin reinforces the arousal system to avert unwanted switches into sleep. Narcolepsy with cataplexy is a disorder of low levels of hypocretin, causing a lack of stability in the "sleep switch," resulting in frequent and unwanted transitions between sleep and wakefulness.

APPROACH TO THE PATIENT WITH SLEEP DISORDERS

Clinical Evaluation

Complaints related to sleep and wakefulness are pervasive in the general population. Approximately 30 percent of adults report one or more symptoms of insomnia including difficulty falling asleep, staying asleep, awakening too early, or nonrestorative sleep. It is estimated that 4 to 21 percent experience EDS at least 3 days per week.[1] Only 6 percent of patients with sleep complaints see a physician specifically for a sleep problem, and many others resort to over-the-counter medications or self-remedies.

Sleep disorders are associated with significant morbidity and mortality. Insomnia, for example, is associated with impairment of all aspects of quality of life including physical functioning, bodily pain, social functioning, and mental health. Obstructive sleep apnea (OSA) increases the risk of cardiovascular and cerebrovascular disease as well as causing motor vehicle accidents.

Individuals with sleep disturbances present with any of four main complaints. The first is insomnia, which may be described as difficulty in falling asleep or staying asleep, having an insufficient amount of sleep, or poor quality of sleep. The second is EDS, which may manifest as feelings of lack of energy or tiredness associated with naps, falling asleep at inappropriate times, or difficulty with concentration or memory. The most common cause of EDS is insufficient time for sleep. The third complaint is of abnormal sleep behavior, usually described by a bed partner. The fourth is of an inability to sleep at the desired time. A single sleep disorder may be associated with multiple complaints.

It is important to understand the motivation of patients in seeking treatment. For example, insomnia may impact job performance and cause a concern for loss of employment. A complaint of snoring may present only after a person is forced to sleep in a separate room to prevent disturbing a bed partner. The International Classification of Sleep Disorders (ICSD) has helped unify the approach to sleep complaints by classifying over 60 sleep disorders.

Patients should fill out a sleep questionnaire and a 1- to 2-week sleep diary. The questionnaire should address the patients' usual sleep hours, nocturnal awakenings, daytime napping, work hours, snoring, daytime functioning, sleep environment, movements in sleep (e.g., leg movements), abnormal behaviors in sleep (e.g., sleepwalking), lifestyle factors (e.g., caffeine intake), weight changes, past medical history, social history, medications, family history of sleep disorders, and other sleep symptoms (e.g., cataplexy or sleep paralysis). A sleep diary should record the time of getting in and out of bed, sleep onset time, awakenings, naps, exercise, sleep medication, and caffeine intake. There are several scales used to assess the degree of daytime sleepiness in a person, such as the Epworth Sleepiness Scale, that can help with diagnosis.

In addition to general medical and neurologic examinations, the physical examination should include the patients' weight, height, body mass index (BMI), blood pressure, and neck circumference. The upper airway should be inspected for pharyngeal narrowing, tonsillar enlargement, uvula enlargement or edema, a large tongue, low-lying palate, and micrognathia, all of which are risk factors for sleep apnea.

Laboratory Testing

POLYSOMNOGRAPHY

The PSG is the most useful diagnostic tool in sleep medicine. Several physiologic variables are recorded during the PSG, including EEG, EMG of the chin and legs, EOG, electrocardiogram, airflow through the nose and mouth, respiratory effort, and oxygen saturation.

The EEG is usually performed using six channels: two frontal leads, two central leads, and two occipital leads. Various stages of sleep are better identified using particular leads, such as identifying delta waves primarily in the frontal leads. A full EEG montage is sometimes used to differentiate parasomnias from epileptiform activity. The EMG of the chin is important in identifying the reduction in muscle tone seen during REM sleep. The EMG of both legs helps capture periodic limb movements (PLMs) in sleep. The EOG is used to identify characteristic eye movements, such as occur during REM sleep. A thermistor or nasal cannula records airflow by monitoring temperature changes. The nasal cannula is attached to a pressure transducer and is more accurate in detecting respiratory changes such as hypopneas. Respiratory effort is recorded using piezoelectric belts around the chest and abdomen in order to differentiate obstructive from central apneas, which are characterized by a complete lack of respiratory effort. A pulse oximeter is usually worn on the finger to monitor oxygen saturation.

The PSG should also include videography to record behavioral changes in sleep, a body position monitor, and snore recording. Sleep is recorded in 30-second intervals termed epochs.

PSG is useful for the diagnosis of sleep-related breathing disorders, narcolepsy, PLM disorder, and REM sleep behavior disorder. When a patient is diagnosed with sleep apnea, the PSG is also used to determine the optimal positive airway pressure (PAP) for treatment; titration can be performed on two separate nights or, alternatively, a split-night study can be performed. During the split-night study, the patient is observed for the first 2 to 3 hours for signs of sleep apnea and, if it is detected, the technician will interrupt the study and begin titration. Certain sleep disorders do not require PSG, such as insomnia, restless legs syndrome (RLS), and circadian rhythm disorders, unless a concomitant breathing disorder is suspected.

MULTIPLE SLEEP LATENCY TEST

The multiple sleep latency test (MSLT) is used to document pathologic daytime sleepiness and to make a diagnosis of narcolepsy or idiopathic hypersomnia. It consists of five nap opportunities each 2 hours apart beginning 2 hours after the termination of the nocturnal PSG. The recording montage consists of the EEG, chin EMG, EOG, and electrocardiogram. Each nap is terminated either 20 minutes after starting (if the patient does not fall asleep) or 15 minutes after the first 30-second epoch of sleep.

The average latency to sleep onset across all five naps is calculated. A mean sleep latency of 8 minutes or less with at least two sleep-onset REM periods strongly suggests a diagnosis of narcolepsy. It is important that the MSLT is performed after at least 6 hours of total sleep time because sleep deprivation can mimic narcolepsy.

MAINTENANCE OF WAKEFULNESS TEST

The maintenance of wakefulness test, a variation of the MSLT, measures a person's ability to stay awake in the daytime. It is useful in determining the effects of treatment on daytime sleepiness and consists of four trials of remaining awake while sedentary every 2 hours, beginning 2 hours after the patient has awakened from nighttime sleep. Each trial is terminated after 40 minutes if the patient remains awake or after the first three consecutive epochs of stage N1 sleep or the first epoch of any other stage of sleep. The mean sleep latency across all four naps is calculated. This test is often used to assess the ability of commercial drivers to remain awake at work.

ACTIGRAPHY

Actigraphy is used to objectively assess the patient's sleep–wake schedule in the normal environment for a 1- to 2-week period. The actigraph is worn on the nondominant wrist and detects small movements to establish periods of rest and activity which equate with wake and sleep. It is most useful in patients with circadian rhythm disorders or insomnia.

HOME SLEEP STUDIES

A home sleep study is a simplified version of a PSG that usually focuses exclusively on respiratory parameters, without measurement of sleep stages. There are various versions, but all should include nasal airflow, respiratory effort, and an oximeter. Home sleep studies can be used in patients with a high pretest probability of having OSA but have a reduced sensitivity for capturing mild cases. In practice, they are used in patients with suspected severe uncomplicated OSA to confirm the diagnosis. The home sleep study is not clinically useful for patients with suspected insomnia, narcolepsy, circadian rhythm disorders, parasomnias, or nocturnal movement disorders.

INSOMNIA

Standardized Definitions

Insomnia is one of the most prevalent health complaints, with 30 to 50 percent of the population reporting transient insomnia. When even more specific diagnostic criteria are utilized, the rates still range between 5 and 20 percent.[2]

Criteria for insomnia differ somewhat between the three main classification systems: International Classification of Diseases, 11th edition (ICD); Diagnostic and Statistical Manual, Treatment Revision, 5th edition

(DSM-V-TR); and International Classification of Sleep Disorders, 3rd edition (ICSD-3). The ICSD-3 classifies insomnia based on duration of symptoms whereas the DSM-V focuses on medical or psychologic comorbidities presenting with insomnia symptoms.

For many years, insomnia was thought of as a symptom of another underlying condition. Classification symptoms all distinguish between forms of "primary" (insomnia occurring without any comorbidities) and "secondary" insomnia (insomnia due to another disorder). Clinical practice has traditionally been to treat the "cause" first, with the belief that insomnia would remit after the underlying condition was addressed. A major shift in this line of thought has taken place in recent years, with a significant amount of research negating the view of primary and secondary insomnia. The relationship between sleep and psychiatric disorders appears to be bidirectional, and causative factors can be extremely difficult to separate from the insomnia itself. The symptom of "nonrestorative" sleep has also been called into question as it is typically related to another sleep disorder that impairs sleep quality.

Risk Factors and Common Comorbidities

Insomnia is most commonly seen in women, older adults, populations with lower socioeconomic status, those with divorce or marital separation, and in those with comorbid psychiatric or medical disorders. Insomnia is commonly observed in neurologic disorders, particularly Parkinson disease, Alzheimer disease, epilepsy, stroke, multiple sclerosis, and traumatic brain injury. Patients with medical conditions such as pain disorders and heart disease are all at increased risk of insomnia.

Consequences

Insomnia is a risk factor for the development of anxiety, depression, substance use, and suicidality. It is also associated with poor attention and concentration, increased work absenteeism, higher medical costs, increased rates of motor vehicle accidents, more falls in the elderly, and reduced overall quality of life.

Clinical Assessment and Diagnosis

The history should focus on symptoms, chronology, exacerbating and alleviating factors, social, medical, and psychiatric precipitants and comorbidities, as well as previous therapies and their success. Symptoms of insomnia range from difficulty in falling or staying asleep to early morning awakenings, or a combination of these symptoms.

TABLE 51-1 ■ Medications and Substances Commonly Associated With Insomnia

- Alcohol
- Caffeine
- Nicotine
- Antidepressants
- Decongestants
- Corticosteroids
- Bronchodilators
- β-Adrenergic antagonists
- Stimulants
- Statins

Understanding a patient's typical sleep—wake periods (on weekdays and weekends) and what the patient does both during the day (including work schedule, napping, and exercise) and in the hours leading up to bedtime and throughout the night is important. A detailed analysis of the patient's thoughts and attitudes about sleep and maladaptive behavioral strategies is crucial to design effective treatment. Symptoms of any other sleep disorders that might impact sleep quality should be assessed, such as snoring, restless legs, apnea, pain, and parasomnias. A medication (prescription and over-the-counter) and substance use history (including time of day taken) is important and should include any caffeine, alcohol, or tobacco use. Table 51-1 lists medications and substances commonly associated with insomnia and Table 51-2 summarizes common comorbid medical conditions.

The most common assessment tools for insomnia include a sleep diary and questionnaires such as the

TABLE 51-2 ■ Medical Conditions Commonly Comorbid With Insomnia

Neurologic: stroke, Parkinson disease, neuropathy, traumatic brain injury

Pulmonary: chronic obstructive pulmonary disease, asthma

Endocrine: diabetes, hypertension

Renal: chronic renal failure

Rheumatologic: rheumatoid arthritis, fibromyalgia, osteoarthritis

Cardiovascular: congestive heart failure, coronary artery disease

Gastrointestinal: gastroesophageal reflux

Insomnia Severity Index and the Pittsburgh Sleep Quality Index. Overnight PSG may be warranted in cases in which a comorbid additional sleep disorder is considered or when treatment for insomnia has been unsuccessful. Actigraphy can be useful for establishing circadian disturbances that may be contributory as well as for tracking sleep–wake times and treatment response.

Pathophysiology

Insomnia is considered a disorder of hyperarousal, with patients demonstrating higher levels of cortisol, increased basal metabolic rates, and the presence of excessive beta or gamma activity on EEG.

The 3P (predisposing, precipitating, and perpetuating) model describes the development and maintenance of chronic insomnia. This model suggests that individuals may be vulnerable to developing insomnia based on predisposing factors that may be biologic (e.g., a diagnosis of chronic pain), psychologic (e.g., a family history of anxiety), or social (e.g., working shifts). Precipitating factors (e.g., a divorce or cancer diagnosis) may start an acute insomnia episode that is followed by behaviors that perpetuate a chronic insomnia, including worrying about sleep or consequences of poor sleep, spending more time in bed in an attempt to catch up on sleep, napping, and using more caffeine, alcohol, or over-the-counter medications.

Treatment

Treatment for insomnia generally involves nonpharmacologic and pharmacologic approaches. Unless a main, obvious underlying cause is found, treatment should focus on insomnia as a separate diagnosis to any other medical or psychiatric issues that may present simultaneously. Nonpharmacologic treatment is always preferred as a first-line intervention, though for many patients a combination of both behavioral and pharmacologic methods may be most beneficial.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is regarded as a highly effective first-line treatment for insomnia. CBT is as effective as the newer benzodiazepine receptor agonists and appears to be more effective in the long term than pharmacologic methods. CBT is as effective in patients with or without comorbid pain, cancer, depression, and anxiety. It improves sleep onset latency, sleep quality, number of awakenings, and total sleep time. It has also been used to help taper off hypnotics; CBT and pharmacotherapy may be started together acutely and then CBT alone may be used chronically following initial gains.

CBT treatments can vary from as few as two 30- to 60-minute sessions to as many as 12 sessions. The core treatment interventions include stimulus control, sleep restriction and sleep hygiene, relaxation training, light therapy, and cognitive therapy.

Stimulus control instructs the patient to use the bed only for sleep and sex, therefore allowing the bed to become conditioned only for those two behaviors. Patients are told to go to bed only when sleepy and to get out of bed if unable to sleep and only return to bed when sleepy again. When out of bed, patients should engage in behaviors that are calm, quiet, and relaxing—all done in dim light without any screen time (e.g., television, cell phones, computers).

Sleep restriction is aimed at minimizing the gap between the amount of time the patient spends in bed and the actual amount of time they are asleep. Patients are advised to select the same awakening time daily (using an alarm) and to allow for a sleep window that approximates the average total sleep time over the past week, but never limiting this to less than 4.5 hours. Sleep hygiene aims to eliminate sleep-incompatible behaviors as described in Table 51-3.

Cognitive therapy teaches patients to challenge maladaptive thoughts and beliefs about sleep, including minimizing worry regarding sleep time and its consequences, and to think realistically about their concerns. Relaxation therapy is helpful for some patients and may include deep breathing or muscle relaxation. Though not routinely used as a part of CBT, strategic use of bright light in the morning or before bedtime may help with some patients who may have a circadian component to their insomnia.

TABLE 51-3 ■ Common Sleep Hygiene Recommendations

1. Keep the same bedtime and wake time every day.
2. Limit liquids, heavy meals, tobacco, and alcohol within 3 hours of bedtime.
3. Limit caffeine at least 8 hours before bedtime.
4. Exercise regularly, but not within 3 hours of bedtime.
5. Wind down for at least 1 hour before bed in dim lights. Engage in something quiet, calm, and relaxing.
6. Keep the bedroom quiet, cool, and dark.
7. Take a hot shower or bath 1.5–2 hours before bedtime, not right before bed.
8. Limit any screen time (TV, tablets, phone, computer) within an hour of bedtime and during the nighttime hours.

PHARMACOLOGIC INTERVENTIONS

Benzodiazepine Receptor Agonists

The medications for insomnia (Table 51-4) approved by the U.S. Food and Drug Administration (FDA) include the benzodiazepines (e.g., temazepam, flurazepam, estazolam, quazepam, triazolam) and nonbenzodiazepine hypnotics (e.g., zaleplon, zolpidem, and eszopiclone). All of the benzodiazepine receptor agonists have been shown to be efficacious and reduce sleep latency with an increase in overall sleep time. There is no single medication that is preferable to any other FDA-approved medication; the pros and cons of each (half-life, cost, past response to treatment) need to be considered with each patient.

These medications are all absorbed rapidly but vary in their half-life. Medications with a longer half-life may be more beneficial for a patient with sleep maintenance and early morning awakening insomnia, whereas a shorter half-life may be preferred for a patient with prolonged sleep-onset latency. Long-acting medications also have a greater risk of daytime somnolence and impaired cognitive functioning, especially in older adults. Newer medications such as zaleplon, zolpidem, and eszopiclone have fewer daytime side effects.

Longer-term efficacy and safety trials with newer nonbenzodiazepines in patients with insomnia have shown continued efficacy with increasing total sleep time and decreasing sleep latency, with overall improvement in daytime functioning and no development of physiologic tolerance. Zaleplon has a short half-life (1 hour) and is best for sleep-onset problems. Zolpidem can increase total sleep time, but the extended-release form also reduces wake time following sleep onset. A newer form of zolpidem (zolpidem tartrate) is fast-acting and aimed at middle of the night awakenings when the patient has at least 4 hours remaining before awakening; taken sublingually, it rapidly dissolves and helps the patient return to sleep. Dosages of this formulation differ based on sex (1.75 mg for women, 3.5 mg for men). Eszopiclone has been found to be effective for both sleep onset and maintenance issues.

Common side effects of benzodiazepines include residual sedation, impaired psychomotor performance, falls, and an increased risk of motor vehicle accidents. Tolerance, abuse, and dependence (especially with benzodiazepines), rebound insomnia, and anterograde amnesia are also concerns. Since these medications can reduce ventilatory drive, caution should also be used in patients with chronic obstructive pulmonary disease or untreated sleep-related breathing disorders.

The newer nonbenzodiazepines do not tend to have physiologic dependence as a concern, though psychologic dependence can develop. These medications most commonly have drowsiness, dizziness, and headaches as reported side effects. Though less commonly reported, amnesia and complex sleep-related behaviors such as sleepwalking or sleep eating have been reported.

TABLE 51-4 ■ Medications Commonly Used for Treatment of Insomnia

FDA-Approved Pharmacologic Treatments

Drug	Dose (mg)	Half-Life (h)	Insomnia Type
Zolpidem	5–10	1.5–2.4	Sleep onset/ maintenance
Zolpidem CR	6.25–12.5	1.6–4.5	Sleep onset/ maintenance
Zolpidem tartrate	1.75–3.5	1.4–3.6	Sleep maintenance
Eszopiclone	1–3	6	Sleep onset/ maintenance
Zaleplon	5–20	1	Sleep onset
Ramelteon	8	1–2.6	Sleep onset
Suvorexant	10–20	12	Sleep onset
Lemborexant	5–10	17–19	Sleep onset/ maintenance
Doxepin	3–6	10–30	Sleep onset
Temazepam	7.5–30	8–15	Sleep maintenance
Estazolam	1–2	10–24	Sleep maintenance
Flurazepam	15–30	48–120	Sleep maintenance
Quazepam	7.5–15	39–73	Sleep maintenance
Triazolam	0.125–0.25	2–6	Sleep onset

Common Off-Label Pharmacologic Treatments

Drug	Half-Life (h)	Side Effects
Amitriptyline	12–24	Dry mouth, dizziness, weight gain
Trazodone	3–14	Dizziness, daytime sedation, constipation
Mirtazipine	13–40	Weight gain, constipation
Quetiapine	6	Elevated liver enzymes, agitation
Olanzapine	20–54	Weight gain, orthostasis
Gabapentin	5–7	Dizziness, ataxia, nausea

Melatonin Receptor Agonists

Ramelteon is an FDA-approved nonbenzodiazepine receptor agonist medication to treat sleep-onset insomnia. It is not a scheduled substance and does not act on the GABA receptors. Rather, it is a selective melatonin agonist that binds to the melatonin receptors MT1 and MT2 in the suprachiasmatic nucleus. Particularly helpful in older adult populations, ramelteon has been shown to help increase total sleep time and reduce sleep latency. Potential side effects include drowsiness, fatigue, nausea, dizziness, and headache. It has also been studied in patients with mild-to-moderate OSA, with no increase in apneic episodes.

Suvorexant is an FDA-approved orexin antagonist used to treat sleep onset and sleep maintenance insomnia. It is the first in a new class of insomnia medications targeted at orexin antagonism. Specifically, suvorexant blocks the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R, which is thought to suppress wake drive. Suvorexant is effective at decreasing sleep latency and increasing total sleep time. Orexin antagonism may also cause potential side effects such as somnolence and mild cataplexy. Other potential side effects include headache, dizziness, and abnormal thinking or behavioral changes. Rebound insomnia may occur upon stopping suvorexant.

Lemborexant, a newer orexin receptor antagonist, was recently approved by the FDA for treating sleep onset and sleep maintenance insomnia. It reduces sleep latency and decreases wake periods after sleep onset, and is not associated with rebound insomnia or withdrawal effects upon discontinuation. Its most common side effects are daytime somnolence and nightmares; complex sleep behaviors, such as sleep walking and sleep driving, also have been reported.

Antidepressant Medications

Low-dose doxepin (3 to 6 mg) has been FDA approved as a treatment for sleep-maintenance insomnia. It is particularly useful for increasing total sleep time and sleep efficiency in patients with primary insomnia. Given their sedating properties, other antidepressants are commonly used (in much lower dosages than for depression treatment). Although limited evidence exists demonstrating efficacy in the treatment of insomnia, practitioners commonly prescribe trazodone, mirtazapine, and amitriptyline because they are perceived as safer than benzodiazepines with a lower potential for dependence. Many patients also have co-existing depression, anxiety, or both, and prescribing physicians feel that these medications may help with both mood and sleep disturbance. Side effects include drowsiness, weight gain, increased suicidal ideation in young adults, dizziness, cardiac arrhythmias, and priapism (with trazodone in particular).

Alternative Medications

Although many patients resort to over-the-counter medications as sleep aids (particularly those that contain diphenhydramine), these medications are not advised in the treatment of chronic insomnia. Atypical antipsychotics (especially quetiapine and olanzapine) are often used off-label to treat both primary insomnia and insomnia comorbid with psychiatric conditions. Case studies have reported effectiveness, particularly with older adults. However, there is a black-box warning regarding the use of antipsychotics in the elderly due to an increased risk of death. Other side effects commonly include weight gain, orthostasis, daytime sedation, agitation, and elevated liver enzymes.

Antiepileptic medications, particularly gabapentin, have also been used to treat insomnia, particularly in patients with comorbid conditions (especially with generalized anxiety disorder, epilepsy, and chronic pain). Side effects include daytime sedation, dizziness, mood changes, and cognitive impairment.

The effects of melatonin taken before bedtime have not been routinely demonstrated, although some reports have suggested decreases in sleep-onset latency. Generally well tolerated by patients, melatonin is not regulated by the FDA and over-the-counter preparations can vary greatly. It is not considered a standard treatment for insomnia and appears to be better suited for treatment of circadian rhythm disorders.

HYPERSOMNIAS

EDS has many implications, including an increased risk of injury at work or home, impaired alertness, increased risk of motor vehicle accidents, and lower overall productivity. EDS can also cause psychologic stress with family, friends, and co-workers.

Narcolepsy

Narcolepsy is a disorder of EDS that is usually associated with cataplexy and other REM phenomena such as sleep paralysis and hypnagogic hallucinations. Sleep regulation and wakefulness are disrupted with rapid transitions between wakefulness and REM sleep, thereby resulting in fragmented sleep and EDS.

Although onset can occur at any age, narcolepsy most commonly begins in the second decade of life, with a second peak seen around 35 years of age. There is a prolonged latency of about 10 years from the time of symptom onset to diagnosis, although improved awareness is shortening this interval. Narcolepsy is usually a sporadic disease with only 1 to 4 percent of cases being autosomal-dominantly inherited.

CLINICAL FEATURES

Excessive Daytime Sleepiness

EDS is the hallmark symptom seen in all patients with narcolepsy and is characterized by a constant baseline sleepiness, along with lapses into sleep throughout the day. Short naps are refreshing, but sleepiness returns within a few hours. Sleep attacks (sudden onset of sleep or the irresistible urge to sleep) can occur throughout the day. Activities that are passive increase the likelihood that sleep will occur, but in severe cases sleep attacks can occur during activities such as talking, standing, eating, or driving. Automatic behaviors (activities where the patient is functionally capable but without recall of the events) are also seen in some patients. For example, a patient can drive to a location without remembering the process of getting there.

Cataplexy

Cataplexy is defined as a sudden loss of muscle tone associated with emotion. It is pathognomonic for narcolepsy, although some patients with narcolepsy do not have cataplexy. Patients often describe knee buckling, head dropping, facial twitching, jaw dropping, or weakness of the arms. Emotions that elicit cataplexy are usually positive, such as laughter, excitement, or joy; they can also be negative, such as anger or frustration. If all striated muscles are involved, patients may fall. However, several seconds of build-up often precede a full attack, so most patients are able to sit down to prevent a fall. Patients may avoid emotional situations, such as social events where cataplexy may occur, affecting quality of life.

Sleep Paralysis

Sleep paralysis is a temporary state of involuntary immobility occurring in transitions between REM sleep and wakefulness. Patients are unable to make gross body movements or speak, but they can open their eyes and are aware of their surroundings. Episodes may last a few minutes and abate either spontaneously or when interrupted by noise or other external stimuli. Sleep paralysis can be frightening, especially when first experienced. Often sleep paralysis is accompanied by hypnagogic hallucinations. About 20 to 50 percent of patients with narcolepsy experience sleep paralysis, but sleep paralysis is also common in the general population.

Hypnagogic Hallucinations

Hypnagogic hallucinations are vivid visual, auditory, tactile, or even kinetic perceptions that, like sleep paralysis, occur during the transitions between wakefulness and REM sleep. Examples include a sensation of impending threat, feelings of suffocation, and sensations of floating, spinning, or falling. Hypnagogic hallucinations occur in 40 to 80 percent of patients with narcolepsy and cataplexy. They are easy to distinguish from the hallucinations occurring in psychiatric disease because patients with narcolepsy usually recognize the events as not real. Psychiatric hallucinations also occur at any time of day, whereas hypnagogic hallucinations surround the sleep period.

Disturbed Nocturnal Sleep

Because narcolepsy is a disorder of EDS, disturbed nocturnal sleep is often overlooked. Patients with narcolepsy typically fall asleep quickly, but have difficulty in maintaining sleep. Frequent arousals are often reported along with difficulty in falling back to sleep. The total amount of sleep in a 24-hour period is the same as in normal individuals; however, it is distributed throughout the day and night, causing daytime sleep attacks and fragmented nocturnal sleep.

Associated Symptoms

Disturbances in memory, concentration, and attention are common in narcolepsy, probably secondary to EDS. REM sleep behavior disorder and PLMs may occur as well. Patients with narcolepsy also report more depressive ideation.

Patients with narcolepsy with cataplexy often have a high BMI or obesity, attributed to metabolic changes resulting from hypocretin loss. A high BMI may also predispose patients to developing OSA; at least 25 percent of patients with narcolepsy have both conditions, which together can worsen EDS, mood, and cognition.

DIAGNOSIS

The differential diagnosis of EDS is shown in Table 51-5. The diagnosis of narcolepsy with cataplexy can be made based on a clear history of EDS and cataplexy. The diagnosis should be confirmed by nocturnal PSG followed by

TABLE 51-5 ■ Differential Diagnosis of Excessive Daytime Sleepiness

Sleep apnea
Behaviorally induced insufficient sleep time
Idiopathic hypersomnia
Recurrent hypersomnia (Kleine–Levin syndrome)
Circadian rhythm disorder, shift work disorder
Metabolic encephalopathy
Drug intoxication or withdrawal
Depression
Epilepsy
Malingering

an MSLT. The diagnosis of narcolepsy without cataplexy can be more difficult and requires a PSG and MSLT.

Nocturnal PSG shows a shortened REM latency in 50 percent of patients. Sleep efficiency is often reduced, with multiple awakenings and an increased percentage of stage N1 sleep. The MSLT should show a mean sleep latency of 8 minutes or less along with two or more sleep-onset REM periods in the setting of sufficient nocturnal sleep.

A less commonly used, but very specific and sensitive method to make the diagnosis is through measurement of cerebrospinal fluid (CSF) hypocretin-1 level, which is less than 110 pg/mL in 90 percent of patients with narcolepsy with cataplexy. Hypocretin loss is now recognized to be the cause of human narcolepsy with cataplexy, and symptoms begin when the majority of hypocretin cells have degenerated.

Narcolepsy is now classified into different types. In type 1, EDS is accompanied either by cataplexy or by low CSF hypocretin levels; in type 2, less severe EDS occurs without cataplexy and with normal CSF hypocretin levels.

PHARMACOLOGIC TREATMENTS

There is no cure for narcolepsy. Treatment goals are to improve quality of life, EDS, and cataplexy as well as other bothersome REM phenomena. A variety of medications can be used to treat these symptoms (Table 51-6).

Excessive Daytime Sleepiness

Modafinil and armodafinil are often used to treat EDS. Sodium oxybate, discussed later, is also effective in treating EDS as well as cataplexy. The various forms of modafinil are effective wake-promoting agents with good safety and tolerability measures and a low abuse potential. Women of childbearing age taking oral contraceptives should use alternative contraception when taking modafinil or armodafinil, as the metabolism of ethinylestradiol may be increased. In the past, amphetamines were the main treatment for EDS; dextroamphetamine, methamphetamine, and combinations of amphetamine salts are helpful with improving daytime alertness, but side effects limit their use.

Solriamfetol is a selective dopamine and norepinephrine reuptake inhibitor now approved by the FDA for the treatment of excessive sleepiness in adult patients with narcolepsy or OSA. Solriamfetol is dosed as a once-daily medication to be taken upon awakening to minimize interference with sleep schedule. Common

TABLE 51-6 ■ Medications Typically Prescribed for Narcolepsy

Drug Name	Dose	Clinical Use	Side Effects
Modafinil (Provigil)	200–400 mg daily in divided dose	EDS	Headache, nausea
Armodafinil (Nuvigil)	150–250 mg daily	EDS	Same as modafinil
Sodium oxybate (Xyrem)	4.5–9 g daily in divided doses	Cataplexy, EDS, broken nighttime sleep	Nausea, vomiting, dizziness
Solriamfetol (Sunosi)	75–150 mg daily	EDS	Headache, anxiety, insomnia
Dextroamphetamine (Dexedrine)	15–60 mg daily	EDS	Irritability, sweating, headaches, tremors
Methylphenidate (Ritalin)	20–60 mg daily in divided doses	EDS	Same as dextroamphetamine
Venlafaxine	75–225 mg daily	Cataplexy	Insomnia, irritability
Pitolisant (Wakix)	17.8–35.6 mg daily	EDS	Headache, nausea, anxiety

EDS, excessive daytime sleepiness.

side effects include headache, nausea, decreased appetite, insomnia, and anxiety.

Pitolisant is a selective H_3 receptor antagonist that increases the synthesis and release of histamine, a wake promoting neurotransmitter. It has recently been approved to treat narcolepsy and is not scheduled as a controlled substance. It significantly decreases EDS. Common side effects include headache, nausea, and anxiety. Pitolisant prolongs the QTc interval, especially in patients with renal or hepatic disease, and should be avoided in patients with known QTc prolongation or cardiac arrhythmias.

Cataplexy

Sodium oxybate is effective in reducing cataplexy as well as EDS. It also reduces other REM phenomena such as sleep paralysis and hypnagogic hallucinations. Due to its sedative properties, it is commonly given in divided doses at sleep onset and then 2 to 4 hours later. Once nightly and low-sodium sodium oxybate are being studied as alternatives to the current formulation of sodium oxybate. Common side effects of sodium oxybate include nausea, vomiting, dizziness, and nocturnal enuresis. If used as recommended, sodium oxybate is safe and has a low risk of dependence or tolerance.

Tricyclic antidepressants were initially the treatment of choice for cataplexy. Medications such as protriptyline and clomipramine are effective, but side effects can be limiting. Newer norepinephrine reuptake inhibitors, such as venlafaxine and atomoxetine, may be more effective and have a more favorable side-effect profile. Selective serotonin reuptake inhibitors (SSRIs) and monoamine-oxidase inhibitors can also be used for cataplexy but are generally less effective.

Disturbed Nocturnal Sleep

Sodium oxybate increases slow-wave sleep and allows patients to sleep more continuously through the night. Newer nonbenzodiazepines such as zolpidem have also been used to consolidate nighttime sleep, but few studies have tested this approach.

NONPHARMACOLOGIC TREATMENTS

Scheduling naps, shifting work periods to times of alertness, avoiding sugar, calculated caffeine use, and following basic sleep hygiene can all benefit patients with narcolepsy. The patient should be advised against driving, bathing, swimming, and using any heavy machinery or household appliances during times of sleepiness. Psychotherapeutic strategies for the management of stressful situations, depression, and anxiety are recommended.

Idiopathic Hypersomnia

Idiopathic hypersomnia is generally less common than narcolepsy, with symptoms beginning in teenagers or young adults. It is typically under-recognized and often a diagnosis made by excluding other causes of EDS.

The primary symptom of idiopathic hypersomnia is EDS despite a full night of sleep and normal sleep architecture; idiopathic hypersomnia includes forms with and without a long sleep time. Patients with long sleep times have at least 10 hours of sleep at night, rarely awaken during nocturnal sleep, have significant difficulty in getting up in the morning, and, unlike patients with narcolepsy, do not find naps to be refreshing. Patients usually report "sleep drunkenness"—difficulty in achieving full alertness upon awakening after a full night of sleep. Patients without long sleep times have less than 10 hours of sleep at night and are less likely to report sleep drunkenness with their EDS. The differential diagnosis of idiopathic hypersomnia is similar to that of narcolepsy.

Nocturnal PSG is routinely performed to exclude other causes of daytime sleepiness and to determine the length of sleep time. An MSLT is also performed, demonstrating EDS with a mean sleep latency of less than 8 minutes and fewer than two sleep-onset REM periods (to rule out possible narcolepsy).

Treatment of idiopathic hypersomnia is similar to that of EDS in patients with narcolepsy, focusing on stimulants and wake-promoting agents, especially modafinil and armodafinil. Positive pharmacologic responses are difficult to achieve. Sleep hygiene, proper diet, and strategic use of caffeine should be utilized. Planned naps and increasing time in bed have not been found to be helpful.

Kleine–Levin Syndrome

Kleine–Levin syndrome is a rare disorder with an estimated prevalence of 1 to 2 cases per million people. Patients are mostly adolescent boys; mean age of onset is 15 years, with some rare cases beginning as early as age 9.[3] Rare familial cases have been reported, with Ashkenazi Jews in the United States and Israel particularly affected. In a majority of cases, the first episode is triggered by a high fever or infection. Disease course typically lasts 8 to 14 years with spontaneous remission in adulthood.

The hallmark symptom of Kleine–Levin syndrome is episodic hypersomnia, with sleep time increasing to over 12 hours per day. Cognitive impairment, apathy, confusion, slowness, derealization, and amnesia are typically seen. Though not reported by all patients, hypersexuality, depressed mood, and hyperphagia may occur. Between episodes, functioning returns to normal with regard to sleep needs, cognitive functioning, and appetite.

Medically based differential diagnoses include alcohol and drug use, multiple sclerosis, temporal lobe seizures, stroke, tumor, Lyme disease, and encephalitis. Typical psychiatric differential diagnoses include depression, bipolar disease, and psychotic disorders. Many patients with Kleine–Levin syndrome first present for psychiatric evaluation.

No standard treatment has been adopted for Kleine–Levin syndrome. When given at the beginning of an episode, amantadine may help to shorten or stop an event. Lithium, lamotrigine, and valproic acid may also be beneficial. Stimulants have shown limited efficacy and may worsen behavioral and cognitive symptoms. Risperidone may help with severe cognitive changes. Family supervision is paramount during episodes. Between episodes, the patient should keep a regular sleep–wake schedule and alcohol and nicotine should be avoided.

SLEEP-RELATED BREATHING DISORDERS

Epidemiology

The estimated prevalence of sleep apnea in the general population ranges between 9 and 85 percent depending on how OSA is defined.[4] Sleep apnea increases in prevalence with increasing age, male sex, and obesity. It is most common in men over the age of 40 years; the incidence in women increases after menopause. Obesity is present in approximately 70 percent of OSA patients. Many nonobese patients have apnea because of the anatomy of their airway, however, and this is underdiagnosed.

Definitions

OSA occurs when there are repetitive episodes of complete or near-complete cessation of airflow during sleep, with continued respiratory effort against a closed airway. These events may cause either a decline in oxygen saturation or a cortical arousal from sleep. Partial reduction in airflow with preserved respiratory effort is defined as a hypopnea.

Obstructive events can occur in any stage of sleep but are most severe during REM sleep, when muscle atonia is present. The pathophysiologies of obstructive apneas and hypopneas are similar and result in the same physiologic consequences. Thus, by PSG they are combined in a single measure known as the apnea-hypopnea index (AHI).

The diagnosis of OSA in adults is made when the AHI is 5 or greater. An index of 5 to 14 is considered to indicate mild OSA; between 15 and 29, moderate OSA; and 30 and above is severe OSA. Generally, the magnitude of the AHI reflects symptom severity; however, some patients may have minimal symptoms but severe sleep apnea on PSG.

Symptoms

Symptoms of OSA are present during both the night and day. Nocturnal symptoms include snoring, gasping or choking, cessation of breathing, frequent arousals, nocturia, excessive movement in sleep, and hyperhidrosis. However, snoring can be the only symptom, and patients are often unaware of any symptoms; it is therefore helpful to interview the bed partner or a family member. Upon awakening, patients often report having a dry mouth, nasal congestion, headaches, or heartburn.

In the daytime, EDS is usually present as a result of respiratory events causing disturbed nighttime sleep. Patients report dozing off when sedentary and have difficulty with concentration and attention, which puts them at increased risk of motor vehicle accidents. Individuals with sleep apnea have a motor vehicle accident rate that is approximately threefold higher than the general population. OSA is particularly concerning in commercial drivers and pilots.

Predisposing Factors

It has been shown in many studies that obesity, particularly truncal obesity, increases the likelihood of sleep apnea. An increase of BMI by 1 standard deviation is associated with a fourfold increase in OSA prevalence.

The prevalence of sleep apnea increases with age, with the steepest increase during the transition from middle to older age. In those older than 65, the prevalence of a sleep-related disorder of breathing ranges from 49 to 90 percent.[4] The ratio of sleep apnea in men and women is about 2 to 1; however, disease prevalence triples in postmenopausal women, even when corrected for BMI.

There may be a genetic predisposition to sleep apnea. The relative risk is between 3 and 5 when parents have OSA and is independent of lifestyle habits. This risk may be due to craniofacial size and shape as well as soft-tissue structures and may explain the higher prevalence found in certain ethnic groups, including Asians and African-Americans. Other structural factors that predispose to OSA include chronic nasal congestion, allergies, deviated nasal septum, tonsillar or adenoid hyperplasia or both, retrognathia or micrognathia, dental mandibular crowding, macroglossia, high-arched palate, enlarged uvula, vocal cord paralysis, increased pharyngeal length, and hereditary craniofacial syndromes such as Pierre Robin syndrome or Treacher Collins syndrome. Additional factors include smoking, alcohol intake, chronic nasal congestion, Down syndrome, acromegaly, hypothyroidism, polycystic ovary syndrome, and neuromuscular diseases.

Physiologic Consequences

During an obstructive apnea or hypopnea, tidal volume and oxygen saturation decline, and carbon dioxide levels rise. Sympathetic tone increases with each event, causing vasoconstriction and often tachycardia that results in increased blood pressure. Other physiologic responses include increased release of inflammatory mediators, elevation of leptin levels, increases in platelet adhesiveness, and raised fibrinogen levels. Generalized endothelial damage also likely occurs.

Pathophysiologic effects of OSA contribute to increases in morbidity and mortality. Several large studies have shown a dose-dependent relationship between sleep apnea and hypertension. Refractory hypertension is a known comorbidity of sleep apnea, and treatment of OSA may lower blood pressure in these patients.

Sleep apnea is also a risk factor for atrial fibrillation[5] and results in a 50 percent reduction in postcardioversion maintenance of normal sinus rhythm after ablation. Studies have shown that untreated sleep apnea increases the risk of coronary artery disease, myocardial infarction, heart failure, cardiovascular mortality, and pulmonary hypertension.[6]

The risk of stroke increases in patients with sleep apnea.[7] This association is most robust in those with moderate or severe sleep apnea. OSA also worsens damage caused by a stroke and increases the risk for subsequent stroke. Sleep apnea after stroke has been shown to worsen cognitive and motor ability.

Clinical Evaluation

PSG should be performed if sleep apnea is suspected. Obstructive apneas are defined as a 90 percent reduction in air flow lasting for at least 10 seconds, with continued inspiratory effort in thoracic and abdominal muscles (Fig. 51-2). This is in contrast to a central apnea, in which there is complete absence of inspiratory effort. An apnea can also be mixed, characterized by initial cessation of both flow and effort, followed by the appearance of effort without flow.

A hypopnea is defined as a reduction of 30 percent or more in flow for at least 10 seconds, associated with a 3 percent oxygen desaturation (Fig. 51-3). Apneas and hypopneas are combined to calculate the AHI.

A respiratory effort-related arousal is characterized by a series of breaths lasting for at least 10 seconds, with flattening of the nasal pressure waveform leading to an arousal from sleep. If esophageal pressure is measured by manometry, it will show progressively more negative

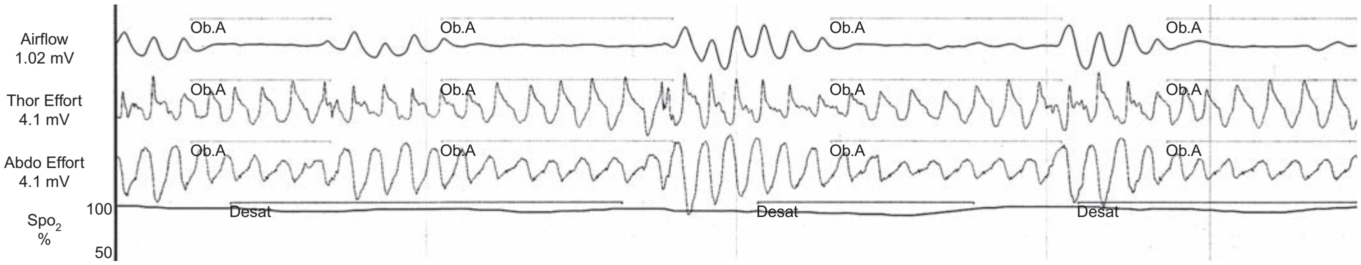


FIGURE 51-2 ■ Obstructive apnea. This 2-min screen shows complete cessation of airflow for at least 10 seconds, accompanied by persisting respiratory efforts of the thoracic (Thor Effort) and abdominal muscles (Abdo Effort). The associated oxygen desaturation (Desat) is not essential for the events to be scored as obstructive apnea (Ob.A). (From Avidan A, Barkoukis T: Review of Sleep Medicine. 3rd Ed. Elsevier, Philadelphia, 2012.)

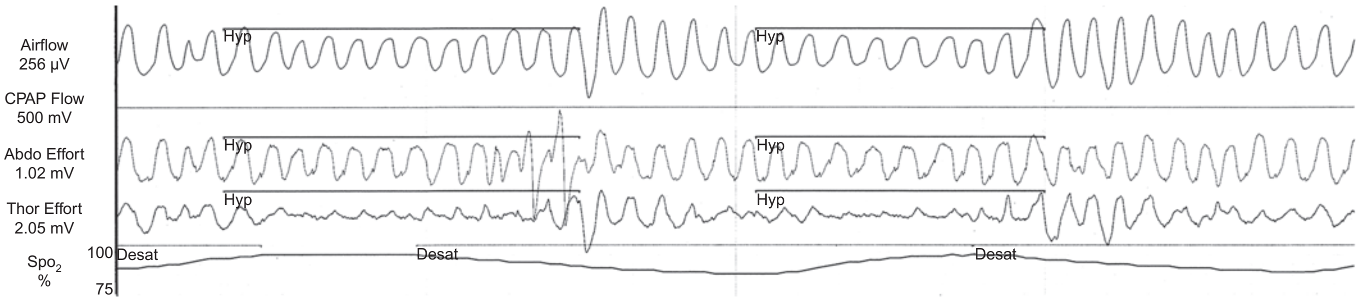


FIGURE 51-3 ■ Obstructive hypopnea (Hyp). This 2-min screen shows airflow reduced by about 50 percent from baseline. There are persisting respiratory efforts of the thoracic (Thor Effort) and abdominal muscles (Abdo Effort), and a decline of more than 3 percent in oxygen saturation. CPAP, continuous positive airway pressure; Desat, desaturation. (From Avidan A, Barkoukis T: Review of Sleep Medicine. 3rd Ed. Elsevier, Philadelphia, 2012.)

pressures preceding the arousal. On PSG the respiratory disturbance index is calculated by combining the total number of apneas, hypopneas, and respiratory effort-related arousals per hour of sleep. Respiratory effort-related arousals are used to identify patients with upper airway resistance syndrome in whom recurrent arousals from sleep occur without clear apneas or hypopneas on PSG. Patients with this syndrome respond to the same treatments as those with OSA.

Treatment

POSITIVE AIRWAY PRESSURE THERAPY

Continuous positive airway pressure (CPAP) is the treatment of choice for OSA. CPAP acts as a pneumatic splint to keep the airway open, thereby preventing obstruction during sleep. It is effective in ameliorating daytime sleepiness, reducing respiratory events, and normalizing oxygen saturation.

Ideally, an in-laboratory CPAP titration should be performed to determine the optimal pressure. CPAP pressures may need to be increased in REM sleep, when the patient is in the supine position, or after ingestion of sedative medications or alcohol. When high pressures are required, bilevel PAP is often used so that patients can exhale against a lower pressure. It is also used in patients who are unable to tolerate CPAP or in those with an element of central hypoventilation. Adaptive servo-ventilation is a noninvasive ventilatory treatment option developed for the treatment of central or complex sleep apnea.

Auto-CPAP devices have been developed to select the optimal PAP without in-laboratory titration. Additionally, auto-CPAP devices can deliver the lowest pressure needed regardless of changes in body position, sleep stage, or weight. Different auto-CPAP algorithms are used depending on the manufacturer. Limitations of these devices include erroneously increased pressure due to leakage and the limited ability to differentiate between central and obstructive respiratory events. Studies to date have shown similar outcomes with CPAP and auto-CPAP therapy.[8]

SURGERY

Young patients with enlarged tonsils, adenoids, or both respond well to surgical intervention. Uvulopalatopharyngoplasty is the most common surgery performed for OSA and includes resection of the uvula, any redundant retroglossal soft tissue, and palatine tonsillar lymphoid tissue. Unfortunately, success—defined as normalization of AHI to less than 10—only occurs in about 33 percent of patients.[9] Approximately 50 percent of patients have a reduction in apneas by more than 50 percent; however, patients with severe sleep apnea are often left with mild to moderate sleep apnea. The most common side effect of the surgery is nasopharyngeal regurgitation of fluid.

Other surgeries that are performed for sleep apnea include septoplasty, rhinoplasty, nasal turbinate reduction, nasal polypectomy, tongue reduction, palatal implants (Pillar procedure), genioglossal advancement or shortening, and maxillomandibular advancement. Relative contraindications to upper airway surgery include morbid obesity and decompensated respiratory or cardiac conditions. In practice, surgery is recommended when patients are unable to tolerate PAP therapy. Surgery is most successful in patients with a low BMI and low AHI.

Upper Airway Stimulation

The hypoglossal nerve stimulator is an implanted device that stimulates the hypoglossal nerve to reduce apneas. The painless stimulation activates the muscles of the tongue, increasing the tone and moving it forward, away from the back of the airway to open the lower pharyngeal airway. The pacemaker-like device monitors breathing pattern and is activated when airflow limitation is detected. Currently the FDA has approved the hypoglossal nerve stimulator for patients older than 22 years with moderate or severe OSA and predominantly obstructive events who have failed or are intolerant to CPAP.[10] Eligible patients should not have complete concentric velopharyngeal collapse on screening sleep endoscopy or any other anatomic findings that would compromise performance of the device. It is not recommended for patients with a BMI exceeding 32 kg/m^2. The most common risks are associated with surgical placement of the device, as well as risk of battery stimulator dysfunction.

Oral Appliances

Oral appliances are dental devices made to maintain patency of the upper airway during sleep. Mandibular advancement devices protrude the mandible forward to increase the luminal area of the airway. Tongue-retaining devices, in contrast, keep the tongue in place, preventing occlusion of the upper airway. Some devices combine these two mechanisms.

Most studies have shown that oral appliances reduce snoring and decrease the number of respiratory events, but do not necessarily normalize them to an AHI less than 5. The most common adverse effects reported with oral appliances include dental discomfort, temporomandibular joint pain, bruxism, gingival irritation, and hypersalivation. These effects are usually mild and self-limited. Contraindications to oral appliances include an inadequate number of teeth (at least 6 to 10 per arch are needed), severe temporomandibular joint problems, inadequate mandibular protrusive ability, and significant bruxism.

Oral appliances are most effective in mild to moderate OSA, in patients with a BMI less than 30, and in patients with supine-dependent OSA.[11]

Behavioral Modifications

The most effective behavioral modification for OSA is weight loss. Lifestyle and dietary modifications, pharmacologic therapy, and bariatric surgery can all be effective in achieving this goal. Studies have shown a 50 percent reduction in AHI with a mean weight loss of 9 percent. Other behavioral interventions include smoking cessation, alcohol avoidance, and increasing time of sleep. Positional therapy (avoiding a supine position during sleep) can be used for patients with supine-dependent OSA. Pharmacologic treatment has not been effective for treating the respiratory events in OSA, but modafinil, armodafinil, and solriamfetol are approved to treat the EDS associated with sleep apnea.

CIRCADIAN RHYTHM DISORDERS

Circadian rhythm disorders develop when there is a persistent or recurrent pattern of sleep disturbance because of alterations in the circadian clock or a misalignment between the endogenous circadian rhythm and the external environment imposed by social or work cycles. The sleep disturbances that arise include insomnia, EDS, or both, and lead to impairments in occupational, social, or other aspects of daily functioning.

Various tools are used to make a diagnosis of a circadian rhythm disorder including the history of sleep and wake patterns, a sleep diary, and actigraphy. Other diagnostic tools that are used more in research than clinical practice include assessment of core body temperature and melatonin levels, the latter increasing approximately 2 to 2.5 hours before sleep onset. The nadir of the core body temperature occurs about 2 hours before habitual wake time.

Delayed Sleep Phase Disorder

Delayed sleep phase disorder is characterized by an inability to fall asleep at the appropriate time at night and an inability to awaken in the morning. This results in a delay of the major sleep period relative to the required sleep—wake time (Fig. 51-4). The patient reports symptoms of sleep-onset insomnia and EDS. If the patient is allowed to sleep at the preferred time, sleep quality and duration are normal and stable.

The prevalence of delayed sleep phase disorder is 0.17 percent in the general population. It occurs most often in adolescence, with a prevalence of 7 to 16 percent. It is estimated that 5 to 10 percent of patients with chronic insomnia in a sleep clinic have delayed sleep phase disorder.

Polymorphisms in the clock genes *hPer3* and *hCLOCK* have been associated with delayed sleep phase disorder.

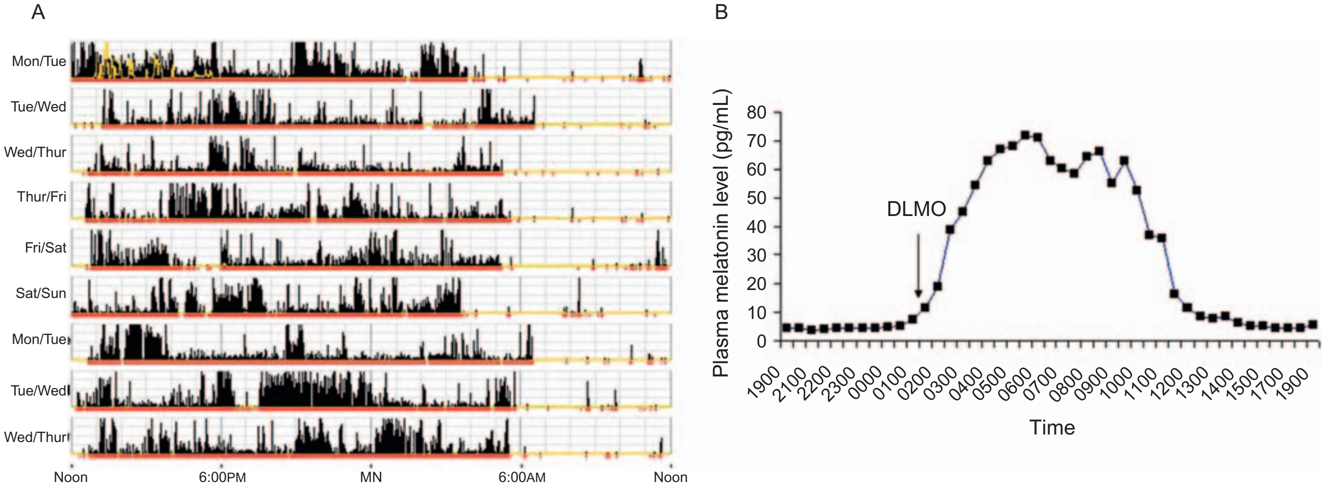


FIGURE 51-4 ■ Actogram of a patient with severe delayed sleep phase disorder (DSPD). *A*, Actogram derived from actigraphy data obtained over 9 days. The yellow lines depict light exposure. The high-amplitude dense bars are representative of wakefulness, and time with little or no activity represents sleep. The average sleep onset is at 5–6 A.M. and wake time is from noon to 1 P.M. Note the stable delay of the sleep–wake rhythm in relation to the conventional sleep time and wake-up time. *B*, The 24-h rhythm of plasma melatonin levels in this patient. The dim-light melatonin onset (DLMO) was defined as an absolute threshold at 10 pg/mL. The DLMO of this patient is delayed, at 1:23 A.M. (which is approximately 5 h later than expected in nondelayed persons).

Additionally, a polymorphism of arylalkylamine *N*-acetyltransferase and an increased frequency of HLA-DR1 are significantly more prevalent in these patients, which may explain the positive family history of such disorder in 40 percent of patients. More recently a mutation in the human clock gene *CRY-1* has been discovered as a cause of familial delayed sleep phase.[12] Environmental factors, such as exposure to bright lights in the evening and lack of light in the morning, can intensify the delayed sleep phase.

Treatment often requires a combination of behavioral techniques, light therapy, chronotherapy, and possibly pharmacologic treatments. Behavioral therapy includes maintaining a regular sleep–wake schedule and proper sleep hygiene. Bright light of 2,000 to 2,500 lux for 2 hours in the biologic morning along with avoidance of bright light in the biologic evening can help achieve earlier sleep and wake times.

Chronotherapy is a technique that involves progressively changing the sleep time by several hours each night until the desired sleep time is reached. It is a highly effective treatment for delayed sleep phase disorder. Compliance is often difficult, however, because it requires individuals to have a flexible schedule. Vacation time is often the best time to try this approach.

Melatonin taken in the early evening decreases sleep latency, increases sleep duration, and improves daytime functioning in patients with delayed sleep phase disorder. Individuals are advised to take 0.3 to 3 mg about 6 hours before their sleep time. Rarely, hypnotics are used to treat delayed sleep phase disorder.

Advanced Sleep Phase Disorder

Advanced sleep phase disorder is a stable advance in the sleep–wake period relative to the desired time. Patients tend to fall asleep early in the night, typically between 6 and 9 P.M., and awaken early in the morning, between 2 and 5 A.M. (Fig. 51-5). Individuals with advanced sleep phase disorder report sleepiness in the early evening, making it difficult to participate in activities at that time. Additionally, early morning insomnia can result in EDS. If patients are allowed to sleep at their endogenous circadian period, their sleep time and quality are normal for age.

Advanced sleep phase disorder is more common in middle-aged and older adults, with an estimated prevalence of about 1 percent. Familial forms of advanced sleep phase disorder exist and should be suspected in younger patients. Mutations in the clock genes *hPer2* and *CSK1D* have been identified.

Treatment recommendations include a combination of bright light exposure in the evening, adhering to a

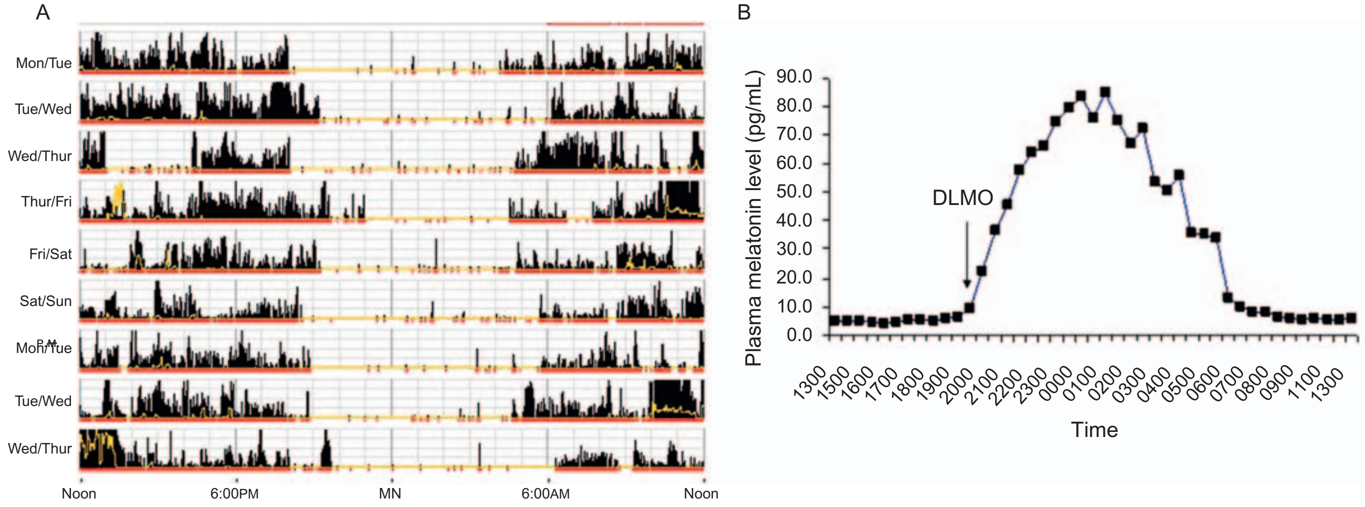


FIGURE 51-5 ■ Actogram of a patient with severe advanced sleep phase disorder. *A*, Actogram derived from actigraphy data obtained over 9 days. The yellow lines depict light exposure. The high-amplitude dense bars are representative of wakefulness, and time with little or no activity time represents sleep. The average sleep onset is 8–9 P.M. and wake time is from 4–5 A.M. Note the stable advance of the sleep–wake rhythm in relation to the conventional sleep and wake-up times. *B*, The 24-h plasma melatonin level rhythm of this patient. The DLMO was defined as an absolute threshold at 10 pg/mL. The DLMO of this patient is advanced, at 7:30 P.M. (which is approximately 2–3 h earlier than expected in nonadvanced persons).

planned sleep–wake schedule, and good sleep hygiene. Studies have shown that bright lights between 7 and 9 P.M. can phase-delay the circadian clock and improve sleep efficiency. Early morning melatonin can theoretically delay the circadian rhythm, but there are no published studies on its efficacy for advanced sleep phase disorder.

Shift Work Disorder

Shift work disorder is a common condition that remains under-recognized and undertreated. It is estimated that 10 percent of shift workers have the disorder. As about 20 percent of the workforce in industrialized countries is employed in some kind of shift work, the prevalence must be high.

Shift work disorder develops when the work schedule occurs during the normal sleep period, resulting in either EDS, insomnia, or both. Difficulty in sleeping occurs when the circadian alerting signal is high, and EDS results from being awake when the circadian alerting signal is low. Additionally, shift workers are often chronically sleep deprived. Night workers sleep between 1 and 4 hours less per night than day workers. Night work and early morning (before 6 A.M.) start times are associated with the most sleep deprivation and greatest wake-time impairments.

Shift work disorder is associated with impairments in performance at work that can have safety consequences, for example, in bus drivers, machine operators, and train conductors. Additional symptoms include chronic fatigue, mood disorders, gastrointestinal problems, as well as disruptions of social and family life. The risks of alcohol or drug abuse, weight gain, hypertension, cardiovascular disease, and breast and endometrial cancer are increased in shift work disorder.

The goals of treatment include realigning the endogenous circadian rhythm with the work schedule and alleviating the insomnia or daytime sleepiness. To achieve circadian realignment, various behavioral interventions can be utilized. The first step includes bright light exposure during the first half of the shift followed by avoidance of bright light about 2 hours before the end of the shift. In addition, wearing dark sunglasses in the morning on the way home from work can improve adaptation. It is important that the room for sleeping is dark and quiet, with a comfortable temperature setting, and that no disturbances occur to interrupt sleep.

To help improve alertness on the job, a short 1- to 2-hour nap about 2 to 3 hours before work can decrease sleepiness. Modafinil and armodafinil are FDA approved for treatment of excessive sleepiness in shift work disorder and significantly improve performance; caffeine is another alerting agent that is frequently used.

Melatonin before bedtime in night shift-workers has been shown to improve sleep duration, but it does not significantly improve alertness. Short-acting hypnotics can also improve symptoms of insomnia associated with shift work disorder.

Jet Lag Disorder

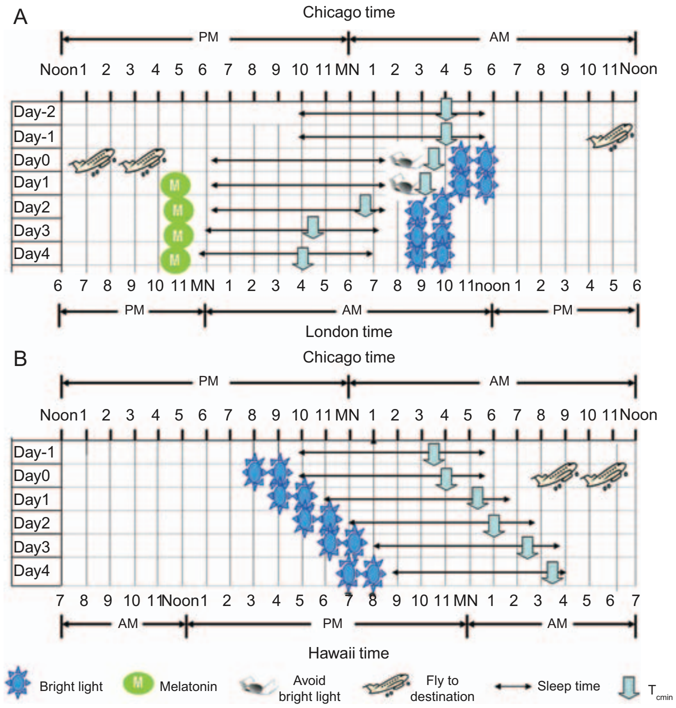
Jet lag develops when there is temporary desynchronization between the internal circadian rhythm and external time cues, resulting in insomnia, daytime sleepiness, and general malaise. Factors that increase the severity of symptoms include the number of time zones traveled and the direction of travel. It is generally more difficult to travel eastward than westward. Symptoms usually resolve within 7 days. Frequent flyers can develop functional impairment requiring treatment.

The goal of treatment is to accelerate realignment of the circadian clock to the new time zone. Circadian adaptation to eastward travel necessitates advancing the circadian rhythm, whereas westward travel requires phase delay. Timed light exposure and exogenous melatonin are recommended (Fig. 51-6). Other behavioral interventions include attempted adjustment to the new time zone before leaving the existing one; avoidance of alcohol, caffeine, and dehydration during travel; and timed naps. Hypnotic agents, such as ramelteon and zolpidem, and agents promoting wakefulness, such as modafinil and armodafinil, improve symptoms of insomnia and EDS, respectively, in jet lag.

Irregular Sleep–Wake Disorder

Irregular sleep–wake disorder is characterized by multiple short sleep and wake periods without a single distinct sleep period. Diagnostic criteria require at least three sleep periods of varying duration in a 24-hour period; however, total sleep time per 24-hour period is normal for age. This results in symptoms of insomnia, excessive EDS, or both. Voluntary maintenance of an irregular sleep–wake schedule must be distinguished from irregular sleep–wake disorder.

This disorder is most commonly seen among institutionalized residents such as those with dementia, mental retardation, and traumatic brain injury. These individuals often lack exposure to external synchronizing cues such as light, activity, and a social schedule. Additionally, neurodegeneration or injury to the central circadian clock system can result in this temporally disorganized sleep–wake schedule.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AM
PM
AM
Hawaii time
Bright light
Melatonin
Avoid bright light
Fly to destination
Sleep time
T_{cmin}

FIGURE 51-6 ■ Strategies to accelerate circadian adaption to jet lag. *A*, An example of a treatment strategy for jet lag associated with an eastward flight over six time zones (from Chicago to London). Adjustment requires an equal number of hours of phase advance. On arrival, the traveler should avoid bright light in the early-morning hours (before 9 A.M.) for the first 2 days so that light does not decrease before nadir of the core body temperature (T_{cmin}), which will induce a phase delay, and exposure to bright light after 9 A.M. to induce phase advances. In addition, melatonin, 1–5 mg taken at 6 P.M. local time on the departure day and at local bedtime (10–11 P.M.) on arrival for 4 days is helpful. *B*, Treatment strategy for jet lag associated with a westward flight over five time zones (from Chicago to Hawaii). The subject should be exposed to as much as light as possible in the late afternoon and early evening at the destination, which will result in the required phase delay.

The goal of treatment for irregular sleep–wake disorder is consolidation of the sleep period, which is best achieved with combination therapy consisting of bright light exposure in the daytime, increased structured activities during the day, avoidance of daytime naps, exogenous melatonin in the evening, reduction of noise and light at night, and institution of a bedtime routine. Melatonin alone has not been shown to help nursing home residents; however, it is effective in children with cognitive problems and irregular sleep–wake disorder.

Non–24-Hour Sleep–Wake Rhythm Disorder

Non–24-hour sleep–wake rhythm disorder (N24SWD) is characterized by a sleep–wake pattern that is not entrained to the 24-hour environmental cycle, usually leading to a delay, over time, of sleep onset and wake times. A lack of synchronization between the endogenous circadian clock and the 24-hour light–dark cycle is the cause. Individuals report complaints of insomnia, EDS, and inability to meet social and occupational obligations.

N24SWD is seen in 50 percent of blind people and is relatively rare in sighted people. Blind individuals with absence of light perception do not receive photic input to the circadian pacemaker, leading to N24SWD. The etiology in sighted people is unclear, but predisposing risk factors include a long circadian period that is beyond the range of entrainment to a 24-hour cycle, psychiatric disorders, and neurodegenerative diseases such as dementia.

Treatment is aimed at establishing stable entrainment of the sleep–wake pattern to the 24-hour external cycle. For patients without light perception, combination therapy is helpful and involves creation of structured social and occupational schedules, maintenance of good sleep hygiene, and low-dose melatonin 1 hour before the preferred sleep time. For sighted patients or those with visual impairment but preserved light perception, timed bright light and melatonin along with the above behavioral interventions are effective.

Tasimelteon was approved in 2014 for the treatment of N24SWD in blind people. It is a selective dual melatonin receptor agonist (MT1 and MT2). By activating melatonin receptors in the suprachiasmatic nucleus, tasimelteon has been shown to improve sleep by resynchronizing the circadian rhythm. Reported side effects include headache, abnormal dreams, urinary and upper respiratory tract infections, and elevated serum alanine aminotransferase.

SLEEP-RELATED MOVEMENT DISORDERS

Sleep-related movement disorders are a category of conditions that involve simple, usually stereotyped, movements that affect sleep. The primary disorders that present to the clinician include RLS and PLM disorder.

Restless Legs Syndrome

RLS is characterized by a compelling urge to move the limbs that is worse during rest, relieved by movement, and is most prominent in the evening or night. The urge to move is associated with distressing sensations in the limbs that are described as creeping, crawling, tingling, burning, or aching. The symptoms most often occur in the legs, but may involve the arms or other parts of the body as well. Approximately 80 to 90 percent of patients with RLS also have PLMs. The condition often has a profound impact on quality of life because of sleep disruptions, including difficulty in initiating and maintaining sleep. The pathophysiology of RLS is not fully understood, but iron-deficiency and central dopaminergic system dysfunction have been implicated.

The estimated prevalence of RLS ranges from 3 to 15 percent; however, the prevalence of clinically significant RLS requiring treatment is 1.6 to 2.8 percent.[13] The female to male ratio is roughly 2:1. Prevalence increases with age, and treatment is often not sought until after age 40. Familial aggregation is common in primary RLS, with a three- to sixfold greater risk for first-degree relatives of patients with RLS. There is also a high concordance rate (83%) in monozygotic twins. At least five different chromosomes (12q, 2p, 14q, 9p, 22p) have been linked to RLS. Secondary RLS is associated with many different medical and neurologic conditions (Table 51-7).

Treatment should begin with behavioral modifications such as improving sleep hygiene with regular sleep–wake times, avoiding caffeine and alcohol, and moderate daily exercise. Iron-deficiency is a common cause of RLS; therefore, serum iron and ferritin levels should be checked before any medication is initiated. Iron replacement should occur when serum ferritin is below 20 ng/mL. Dopamine agonist or alpha$_2$ delta calcium-channel ligands are considered first-line pharmacologic therapy for patients who do not respond to behavioral management or iron supplementation (Table 51-8).

Dopamine agonists alleviate the symptoms of RLS in 70 to 90 percent of patients with low doses and have less risk of augmentation than levodopa. Pramipexole is a nonergot-derived D3 and D2 receptor agonist that has proven efficacy for RLS at daily doses of 0.25 to 1 mg. Ropinirole is another nonergot-derived D3 and D2 receptor agonist that is effective for RLS at a mean dose of 2 mg daily. Plasma concentrations of ropinirole and pramipexole peak almost 2 hours after ingestion; therefore, it is important to dose them several hours before symptom onset. Ergot-derived dopamine agonists are not considered first-line treatment because of the risk of pulmonary fibrosis and valvular heart disease.

TABLE 51-7 ■ Secondary Causes of Restless Legs Syndrome

Medical

- Iron-deficiency anemia
- End-stage renal disease
- Rheumatologic disorders
- Diabetes
- Obstructive sleep apnea
- Liver disease
- Chronic obstructive pulmonary disease
- Celiac disease
- Gastric bypass surgery
- Crohn disease

Neurologic

- Neuropathy
- Parkinson disease
- Spinocerebellar ataxia types 1, 2, 3
- Multiple sclerosis
- Migraines
- Myelopathies

Medications

- Antihistamines
- Neuroleptics
- Metoclopramide
- Proton pump inhibitors
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Lithium
- Mirtazapine

Lifestyle

- Sleep restriction
- Smoking
- Alcohol
- Caffeine
- Too little or too much physical activity

TABLE 51-8 ■ Pharmacologic Therapy for Restless Legs Syndrome

Drug	Dose (mg)	Cautions
Dopaminergic Agents		
Levodopa	100–200	Augmentation, rebound, tolerance
Pramipexole	0.25–1	Sleepiness, impulse control impairment
Ropinirole	0.25–2	Sleepiness, impulse control impairment
Rotigotine patch	0.5	Augmentation, skin reaction
Alpha$_2$ Delta Calcium-Channel Ligands		
Gabapentin	600–2,400	Somnolence, renal impairment
Pregabalin	75–300	Angioedema, renal impairment
Gabapentin enacarbil	600	Somnolence, renal impairment
Other		
Oxycodone	5–20	Abuse potential, dependence
Tramadol	50–200	Augmentation, withdrawal
Clonazepam	0.25–1	Withdrawal, dependence
Zolpidem	5–10	Complex sleep-related behaviors

Adverse effects associated with dopamine agonists include nausea, headache, somnolence, and dizziness.

Transdermal dopamine agonists have been approved as an alternative treatment of RLS. Rotigotine, in patch form, has good long-term safety and efficacy data. The rationale for continuous drug administration is to maintain a more steady plasma level, thus benefiting patients with daytime symptoms of RLS.

Alpha$_2$ ligands, such as gabapentin, pregabalin, and gabapentin enacarbil, are also effective treatments for RLS and PLMs. Alpha$_2$ ligands can be particularly helpful in patients with painful RLS or those with concomitant neuropathic pain, insomnia, impulse control disorders, or addiction associated with the use of dopamine agonists. However, dopamine agonists are preferable in patients with severe RLS, depression, obesity, or metabolic syndrome.

The mean effective daily dose of gabapentin is around 1,800 mg/day, divided into two daily doses; however, doses up to 2,400 mg/day may be necessary. Pregabalin has been shown to be effective for RLS as well at a mean effective dose of around 125 mg/day. Gabapentin enacarbil, at a single dose of 600 mg/day, has been shown to have superior absorption and longer duration of action when compared to gabapentin.

Other medications that have shown some efficacy in relieving symptoms of RLS include oxycodone, tramadol, clonazepam, levodopa, and zolpidem. The side-effect profiles of these medications limit usage; however, they should be considered when first-line therapy fails or as adjunct therapy. Levodopa was initially used for RLS; however, its use is limited by rebound, tolerance, and augmentation (the occurrence of more severe RLS symptoms that develop earlier in the evening).

Periodic Limb Movements

PLMs are repetitive stereotyped limb movements occurring during sleep. PLMs usually occur in the lower extremities but can involve the arms. The stereotyped movements frequently consist of extension of the big toe with partial flexion of the knee and ankle. Movements may cause an autonomic or cortical arousal or an awakening.

Patients are often asymptomatic, with only the bed partner reporting the abnormal movements. PLMs can be present in many sleep disorders, such as RLS and narcolepsy. Often they are an asymptomatic finding during a sleep study.

PLM disorder is characterized by the presence of PLMs along with sleep disruption not otherwise caused by another sleep disorder. Sleep disruption from PLMs can present as daytime sleepiness or insomnia.

If PLMs are found to be part of another sleep disorder, such as RLS, then the primary sleep disorder should be treated. PLMs must be differentiated from PLM disorder in order to discern whether treatment is needed. The same medications that are used for RLS have been shown to alleviate PLMs.

PARASOMNIAS

Parasomnias are disorders characterized by abnormal behavioral or physiologic events, or both, that accompany sleep-specific sleep stages, or sleep–wake transitions. These events typically occur because of inappropriate timing of the sleep cycles. Physiologic and behavioral manifestations include activation of the central nervous system, with skeletal muscle activity and associated autonomic changes, resulting in undesirable or unwanted motor or verbal phenomena during sleep. Parasomnias can lead to disrupted sleep, poor health outcomes, psychosocial problems, and even cause physical harm in more severe cases. They are typically classified based on the state in which they occur—REM sleep, NREM sleep, or both sleep states.

NREM Parasomnias

Disorders of arousal during NREM sleep include sleepwalking, sleep terrors, and confusional arousals. Thought to occur due to the instability of slow-wave sleep, arousal disorders are built on the premise that the arousals are not an all-or-none phenomenon, but rather a continuum of reestablishment of full alertness, orientation, judgment, and control over behavior; a rapid alteration of sleep and waking states; or both.

Sleepwalking (Somnambulism)

Sleepwalking refers to a series of multifaceted motor behaviors that are initiated during slow-wave sleep and result in walking during a state of altered consciousness within the first third of the sleep period. Most prevalent in children between 5 and 10 years old and less common in older groups, sleepwalking episodes range from subdued to sophisticated, including unlocking doors, texting, dressing, and driving. They range in duration from 15 seconds to 30 minutes, and recall may be limited or absent. The walker's eyes are open and behaviors may be clumsy. When awakened, the walkers typically respond with simple responses ("had to take a shower"). Sleepwalking in adults can be dangerous as it can be associated with violent or dangerous activity. Sleepwalking patients are generally neurologically normal, but other sleep disorders should be excluded.

Confusional Arousals

Confusional arousals are brief, impaired, and incomplete arousals that typically begin during slow-wave sleep. The individual typically looks confused, especially in the early part of the night. Confusional arousals differ from sleepwalking in that the affected patient does not leave the bed. Most commonly seen during the first third of the night in slow-wave sleep, such arousals can also occur in other NREM sleep stages or the later part of the night. Common examples include sitting up in bed with simple vocalization or picking at bedclothes.

Anxiety, sleep deprivation, fever, and endocrine factors (e.g., pregnancy) may increase the frequency of episodes. Other precipitating factors include alcohol or hypnotic consumption, antihistamines, and lithium. Primary sleep disorders (e.g., apnea or periodic leg movements) may also exacerbate confusional arousals.

Sleep Terrors

Sleep terrors (night terrors, pavor nocturnus) are less common than sleepwalking, beginning with an incomplete arousal from slow-wave sleep. Often associated with a frightening image and autonomic activation, a typical event might terrify the patient, who often emits an abrupt piercing scream and has autonomic and behavioral manifestations of intense fear. Usually associated with agitation, sweating, tachycardia, and hyperpnea, sleep terrors are more common in children than adults. Episodes occur in the first third of the night, with the patient having no or very little recall of the event the next morning. Witnesses tend to be more distressed by the events than patients. Children who present with sleep terrors often grow out of them, but events may continue to be precipitated by alcohol use, stress, sleep deprivation, and shift work. Adults presenting with sleep terrors should be assessed for psychiatric disorders.

TREATMENT OF AROUSAL DISORDERS

Management of arousal disorders should involve reassurance and education, especially in children. Symptoms generally do not require intervention and events will usually minimize with time (in children). Although stress or psychiatric issues may be a factor, it should not be the clinician's first assumption as to etiology. Proper clinical management involves the recommendation of sleep hygiene including avoidance of alcohol and drugs, maintenance of a consistent sleep—wake schedule, and reduction of bedroom light and noise. Sleep deprivation should be avoided. The environment should be kept safe to avoid injuries from arousals.

It is often difficult to arouse individuals from slow-wave sleep episodes. When aroused, patients may be confused or even aggressive, with subsequent amnesia for the episode. Scheduled awakenings (awakening the patient 15 minutes before each usual arousal on a regular basis) have been effective.

Stress-management skills, psychotherapy, and hypnosis have also been found useful. Pharmacologic treatment is necessary when events are frequent, put the family or patient at risk of being harmed, or disturb family life (Table 51-9). Benzodiazepines (used continuously or as needed), tricyclic antidepressants, and SSRIs (such as paroxetine) have been successfully used in treatment, though controlled trials are sparse.

TABLE 51-9 ■ Pharmacologic Treatment of Parasomnias

Medication	Effective Dose Range (mg)	Appropriate Patient Population
Non-REM Parasomnias		
Clonazepam	0.5–2.0	First-line treatment
Triazolam	0.125–0.5	First-line treatment
Paroxetine	20–40	Alternative treatment
Zolpidem	5–10	Alternative treatment
Sleep-Related Eating Disorders		
Clonazepam	0.5–2.0	First-line treatment
Lorazepam	1.0–2.0	Side effects with clonazepam
Pramipexole	0.5–1.0	Unresponsive to benzodiazepines, history of substance abuse
Melatonin	3–15	Unresponsive to benzodiazepines, history of substance abuse
REM-Related Parasomnias		
Clonazepam	0.5–2.0	First-line treatment for RBD
Melatonin	3–12	May be effective in RBD
Prazosin	5–15	Nightmares in PTSD
SSRI (e.g., Sertraline)	50–200	History of daytime eating, mood, anxiety disorder
Pramipexole	0.18–0.36	RBD with Parkinson disease
Topiramate	25–400	Binge eating disorder, *insomnia*

RBD, REM-sleep behavior disorder; PTSD, post-traumatic stress disorder.

REM Parasomnias

NIGHTMARES

Nightmares are unpleasant dreams that awaken the individual from REM sleep and are often associated with strong emotions such as fear, anger, sadness, or embarrassment. Although they may occur at any part of the night, they predominantly occur during the final third, when REM sleep is more prominent. Recall is generally vivid and detail oriented. Nightmare disorder can be idiopathic or related to an underlying condition, with recurrent nightmares often linked to psychologic trauma or psychiatric disorders (e.g., post-traumatic stress disorder, affective disorders). Frequent nightmares can lead to disturbed sleep-onset latency, awakenings, restless sleep, insomnia, and a lower overall quality of life.

Although usually seen in children, adults may also experience nightmares that are recurrent, frequent, or both, with causes typically related to stress, post-traumatic stress disorder, antidepressant or antihypertensive medications, withdrawal from alcohol or drugs, narcolepsy, and sleep-related breathing disorders.

Patients should be told to avoid alcohol, drugs, and heavy meals at least 3 hours before bedtime. Clinicians should also assess for any medications or other sleep disorders (e.g., sleep apnea) that might exacerbate nightmares. Though more commonly used to treat hypertension, prazosin is effective as a routine treatment, particularly in post-traumatic nightmares. Imagery rehearsal therapy has shown promising results for nightmare treatment. Patients are taught to "change the dream in any way they wish" and imagine the new dream for 5 to 20 minutes daily.

REM Sleep Behavior Disorder

REM sleep behavior disorder is characterized by forceful motor activity that typically occurs during REM sleep in the absence of the usual muscle atonia. It often involves behaviors dangerous to self or the bed partner, along with unpleasant images or dreams. REM sleep behavior disorder is more frequent in men than women and typically occurs in the middle-aged or elderly. The prevalence is estimated as 0.5 percent. PSG can exclude seizure activity and confirm the presence of increased EMG tone during REM sleep. REM sleep behavior disorder can be idiopathic or related to underlying neurologic conditions (e.g., synucleinopathies), and patients should undergo a thorough physical examination seeking any comorbidities that might interrupt REM sleep.[14] In some patients, REM sleep behavior disorder precedes the development of a synucleinopathy such as Parkinson disease by many years. Acute REM sleep behavior disorder can be induced by medications (e.g., monoamine oxidase inhibitors, SSRIs), benzodiazepine withdrawal, and alcohol.

Measures should be taken to keep the sleep environment safe. The patient should sleep in a separate bed from their partner until events are controlled. Patients usually respond well to clonazepam (0.5 to 2.0 mg). Melatonin, hypnotics, and dopaminergic medications may also be effective in some cases.

Other Parasomnias

Sleep-Related Eating Disorder

Sleep-related eating disorder involves partial arousals from sleep where patients engage in involuntary eating and drinking. It has a higher prevalence in patients with a history of eating disorders or sleepwalking, and can be linked to medications (e.g., zolpidem, anticholinergics, and lithium). Patients may have unexplained weight gain and morning anorexia. They have limited or no memory of events, and foods consumed can even be toxic, inedible, or peculiar such as coffee grounds, frozen or uncooked products, cake mix, eggshells, or cleaning materials. Patients should be evaluated for comorbid sleep disorders such as PLMs and OSA. Topiramate and dopaminergic medications have been effective in some patients.

Sexsomnia

Sexsomnia is characterized by abnormal sexual behaviors during sleep, with patients having little to no memory of the event. Sexual arousal may be accompanied by autonomic activation (e.g., nocturnal penile tumescence, nocturnal emission, vaginal lubrication, and dream orgasm). Many patients have a history of sleepwalking; comorbid sleep disorders should be evaluated. Patients are advised to optimize proper sleep hygiene.

Forensic Implications

Violent behaviors may occur during sleep without conscious awareness, leading to important forensic implications. Behaviors such as murder, assault, or apparent suicide can be linked to disorders of arousal, REM sleep behavior disorder, psychogenic dissociative states, and sleep-related seizures. These sleep-related episodes have been reported in 2 percent of the population, but more prevalence and treatment studies are needed.

Exploding Head Syndrome

Occurring during the switch from wakefulness to sleep, patients may be awakened by the sensation of a loud, explosion-like bursting in the head. Most are usually painless, but patients occasionally note a small stab of pain accompanying the sound. Sleep deprivation and stress often worsen these events, and optimizing sleep hygiene and reassurance that these events are benign are all that is required for treatment.

SLEEP DISORDERS IN PATIENTS WITH NEUROLOGIC DISORDERS

Sleep complaints are common in patients with neurologic disorders. Untreated sleep conditions often worsen neurologic symptoms and increase morbidity and mortality. Neurologists can play a central role in diagnosing these disorders and thereby improve the care of these patients.

Parkinson Disease

Sleep disturbances are common in Parkinson disease, affecting as many as 60 to 98 percent of patients. Common symptoms include difficulty in falling asleep and staying asleep, abnormal movements in sleep, and EDS. Sleep disturbances develop for multiple reasons including: (1) degeneration of the cortical sleep centers that regulate the sleep–wake cycle; (2) side effects of dopaminergic and anticholinergic medications; (3) rigidity, bradykinesia, and dystonia resulting in difficulty in shifting positions during sleep, leading to frequent arousals and sometimes pain; (4) depression and anxiety resulting in insomnia; (5) altered muscle tone in the upper airway facilitating sleep apnea; and (6) dream enactment behavior such as REM sleep behavior disorder. The severity of Parkinson disease is directly related to the severity of the sleep disturbances.

It is helpful to interview the patient in the presence of a close friend or family member when screening for sleep disorders as patients often lack insight into their sleep disturbances. Clinical tools such as the Parkinson Disease Sleepiness Scale or the Epworth Sleepiness Scale can assess need for and response to therapy. Multiple treatment strategies are often needed including medication adjustments, behavioral modifications, and therapy of specific sleep disorders.

Alzheimer Disease

Sleep disturbances are common in dementia and may worsen cognitive function and mood. Additionally, sleep disruption can worsen caregiver burden and serve as a primary reason for institutionalization. Treatment of sleep disorders can improve cognitive functioning in these patients.

Irregular sleep–wake disorder is the most common sleep problem in Alzheimer disease and typically presents with insomnia at night and EDS.[15] The etiology involves degeneration of the suprachiasmatic nucleus in the hypothalamus and dysregulation of the pineal gland and its melatonin output. Although melatonin levels are lower in Alzheimer disease patients than age-matched controls, studies have not shown a benefit of melatonin supplementation in these patients.

A major factor in the development of irregular sleep–wake disorder in Alzheimer disease is lack of appropriate zeitgebers, such as light and physical activity, which are essential for establishing a regular circadian rhythm. Dementia patients, especially those in nursing homes, frequently lack proper light exposure and physical activity. Behavioral interventions include ensuring adequate activity and light during the daytime and minimizing stimulation and disruptions at night.

Sundowning, defined as agitated behavior that appears in the late afternoon or early evening, is common in Alzheimer disease and other forms of dementia. The exact cause is unknown, but it may be due to changes in melatonin secretion, alterations in the cholinergic projections from the nucleus basalis of Meynert, delay in the body temperature rhythm, or degeneration of the suprachiasmatic nucleus. Behavioral interventions, such as maintaining a regular schedule in a known environment with familiar caregivers, can minimize sundowning. Eliminating delirium-provoking medications is also important.

The presence of other primary sleep disorders such as OSA should be assessed. Treatment of OSA can improve cognitive functioning and sleep disturbances in patients with Alzheimer disease. Patients with dementia are generally able to tolerate CPAP therapy as well as other patients.

Epilepsy

The relationship between sleep and epilepsy is bidirectional. Epilepsy and some of the medications used in its treatment can disturb nocturnal sleep and daytime alertness. Additionally, sleep deprivation and sleep disorders can increase the likelihood of having seizures in a predisposed individual, highlighting the need for proper sleep hygiene in patients with epilepsy.

Patients are often unaware of seizures that occur during sleep. They may report daytime sleepiness, difficulty with concentration, or awakenings, which may be misinterpreted as insomnia. Patients with epilepsy have more sleep fragmentation and sleep stage shifts than those without seizures. Antiepileptic medications such as carbamazepine, levetiracetam, phenytoin, phenobarbital, and topiramate can produce hypersomnolence.

Sleep also influences EEG activity, with increased expression of ictal and interictal discharges during NREM sleep. During NREM sleep, the EEG shows synchronous oscillation of cortical neurons that generate sleep spindles, K complexes, and slow waves that promote seizure propagation. As a result, some patients with epilepsy only have seizures during sleep. Conversely, REM sleep is characterized by EEG desynchronization that inhibits epileptiform discharges.

There is a higher prevalence of OSA in patients with epilepsy, especially in those with medically refractory seizures. OSA likely increases the frequency of seizures due to a combination of recurrent oxygen desaturation, sleep fragmentation, and sleep deprivation. Treatment of sleep apnea tends to improve seizure control, cognitive performance, and quality of life in these patients.

Parasomnias can be difficult to differentiate from certain types of epilepsy such as nocturnal frontal lobe epilepsy. Additionally, these two disorders may co-exist in the same patient, highlighting the need for overnight video-EEG and PSG to make a definitive diagnosis. Recent studies have found NREM parasomnias to be more frequent in sporadic and familial forms of nocturnal frontal lobe epilepsy, perhaps due to the two disorders sharing underlying genetic mutations.

Stroke

Sleep apnea is an independent risk factor for hypertension and cardiovascular and cerebrovascular disease. This link is thought is be secondary to increased sympathetic activity in sleep, which influences heart rate and blood pressure. Additionally, proinflammatory vascular risk factors, oxidative stress, and endothelial damage are increased in OSA. Studies also suggest that sleep apnea is a risk factor for new-onset atrial fibrillation, and increases the chance of postablation failure. Other studies have suggested that sleep apnea increases the risk of stroke upon awakening in those with a patent foramen ovale.

Sleep apnea may lead to cognitive decline by increasing small-vessel disease due to systemic chronic hypoxia and sympathetic stress. CPAP treatment may help to prevent cognitive decline in these circumstances.

Sleep apnea is common in patients after stroke and is associated with poorer functional outcome, cognitive functioning, and performance of activities of daily living, along with depressed mood. Data have shown benefit from CPAP use following stroke in those with OSA.[15]

Headache

Studies have established a strong association between sleep disorders and most primary headache types including migraine, tension, cluster, hypnic, and morning headaches. Conversely, sleep dysregulation caused by most sleep disorders, including insomnia, sleep apnea, hypersomnia, and circadian rhythm disorders, increases the risk of chronic daily headaches. Insomnia is the most common sleep disorder found in patients with migraine and tension-type headaches, and depression and anxiety may be associated. Headache histories should therefore always include a screen for sleep disorders.

Headaches that emerge out of sleep have been linked to sleep apnea. OSA increases the relative risk of chronic headache two- to threefold, and the risk of cluster headache eightfold. Studies have shown headache improvement with CPAP use.

Both oversleeping and sleep deprivation are known triggers for migraines. Sleep duration of less than 6 hours and more than 8.5 hours has been associated with increased headache intensity. The optimal sleep duration to reduce headaches in these patients is likely around 7 to 8 hours.

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SECTION

13

Psychogenic Disorders

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CHAPTER

52

Functional (Psychogenic) Neurologic Disorders

CARINE W. MAURER ■ MARK HALLETT

INTRODUCTION
CLINICAL FEATURES OF FUNCTIONAL NEUROLOGIC DISORDERS
  Motor Disorders
  Axial Disorders
  Nonepileptic Seizures
  Speech and Voice Disorders
  Sensory Symptoms
  Functional Dizziness
DIAGNOSTIC CRITERIA
ETIOLOGY
PATHOPHYSIOLOGY
TREATMENT
  Delivery of the Diagnosis
  Psychologic Treatment
  Motor Rehabilitation
  Other Treatment Options
  Multidisciplinary Approach

INTRODUCTION

A functional neurologic disorder (FND) is any type of neurologic disorder that arises from dysfunction of the brain when normal function is possible.[1] The name of this disorder has changed over the years. Previously called *hysteria* and *conversion disorder*, it then became *psychogenic neurologic disorder*, and only in recent years has the terminology changed to *functional neurologic disorder*. The change is due to several factors. First, while psychologic factors often seem etiologically relevant, such factors cannot always be identified, and the pathophysiology is not fully understood. Second, patients are more accepting of the diagnostic label, and acceptance of the diagnosis is the first step in treatment.

FNDs fall between neurology and psychiatry. Patients present to neurologists with neurologic symptoms, but the usual treatments have been psychiatric. Neither specialty took an interest in these patients, who were largely neglected in the latter part of the twentieth century when neither neurologists nor psychiatrists were being trained to diagnose and treat them. Fortunately, the situation is changing. In the psychiatric classification DSM-5, “functional neurologic symptom disorder” or “conversion disorder” falls under somatic symptom and related disorders. To make the diagnosis, manifestations need to be inconsistent and incongruent with other neurologic disorders and cause the patient distress. Such formal recognition is important.

FNDs are common. Neurologic practices vary, but typically FND is the second most common diagnosis after headache, accounting for 10 to 30 percent of patients.[2] Women are affected more often than men. The diagnosis in the past was largely based on excluding other neurologic disorders, but the emphasis now is on the identification of positive features. FNDs may accompany other neurologic disorders, thus complicating their diagnosis. For example, many patients with multiple sclerosis also have functional symptoms, and patients with an established seizure disorder can also have functional seizures.

CLINICAL FEATURES OF FUNCTIONAL NEUROLOGIC DISORDERS

As with any other neurologic disorder, the key to diagnosis of FND involves careful assessment of findings detected on neurologic examination, combined with clues from the clinical history. Of critical importance is

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that the diagnosis of FND is made on the basis of positive findings, not merely one in which other "organic" diseases are excluded (Table 52-1). Positive findings suggestive of a diagnosis of FND are discussed below.

TABLE 52-1 ■ Positive Signs on Neurologic Examination in Functional Neurologic Disorders

General Features

- Inconsistency
- Distractibility
- Suggestibility

Functional Weakness

- Drift without pronation
- Hoover sign
- Collapsing/give-way weakness

Functional Parkinsonism

- Excessive slowness without decrement in speed or amplitude on repetitive tapping
- Variability in tone during passive manipulation

Functional Tremor

- Variable frequency
- Entrainment or suppressibility of tremor with externally cued movement
- Pause with contralateral ballistic movement

Functional Dystonia

- Resistance to passive manipulation
- Lack of sensory trick
- Face region: tonic lateral deviation of lips or jaw to one side
- Face region: concurrent contraction of orbicularis oculi and contralateral frontalis

Functional Gait/Posture

- Better balance than claimed
- Excessive gait slowness
- Dragging monoplegic gait
- Knee buckling
- Absence of falls despite excessive sway during gait
- Excessive demonstration of effort
- Inconsistent, noneconomic posture

Functional Speech and Voice

- Effortful speech
- Excessive variability in severity during different speech examination activities

Functional Sensory Symptoms

- Splitting of vibration across forehead or sternum
- Precise midline splitting of sensory deficit
- Tubular visual field defect

Motor Disorders

Features suggestive of functional motor disorders include an abrupt onset of symptoms and inconsistency of the abnormal movements. Symptoms may rapidly vary in terms of severity, disappearing with distraction and increasing with attention. Diagnosis is based upon demonstration of motor inconsistency (i.e., varying symptoms with susceptibility to distraction) and/or incongruence (i.e., movements that are incompatible with normal physiologic patterns).

Several features on neurologic examination can point to a diagnosis of functional weakness. Drift without pronation of the weak arm, Hoover sign, dragging monoplegic gait, and collapsing or give-way weakness are all positive signs suggestive of functional weakness.[3] Hoover sign relies on contralateral synkinetic oppositional mirror movements, and is deemed to be positive when weakness of hip extension is corrected upon flexion of the contralateral hip against resistance. Dragging monoplegic gait describes a gait in which the leg is dragged with the knee extended and the ipsilateral hip either externally or internally rotated; this contrasts with the circumduction observed in the setting of organic leg weakness. Collapsing or give-way weakness describes the demonstration of strength followed by sudden collapse. It is important to note that the validity of these signs is variable. Collapsing weakness, for example, can also be seen in patients with pain or with difficulty following instructions in addition to those with functional weakness.

Functional excess movements can include functional tremor, dystonia, and myoclonus, among others. Functional tremor is characterized by its variable frequency and distractibility. The "entrainment test" is commonly used in the diagnosis of functional tremor and highlights its variable frequency. In this maneuver, the patient performs an externally cued rhythmic movement, with resulting suppression or altered frequency of the functional tremor. Features suggestive of functional dystonia include abrupt onset, fixed posture present from early in the course of the disease, and resistance to manipulation. Pain commonly accompanies functional dystonia, and sensory tricks are rare. Functional dystonia involving the cranial region can present with lateral deviation of the mouth, including the lower lip, jaw, and tongue. When functional dystonia involves the eye, spasm of the orbicularis oculi with contraction of the contralateral frontalis muscle may be seen.[1]

Functional parkinsonism can present with excessive slowness in the absence of decrement of repetitive movements, as well as normal speed when spontaneous movements are performed. Inconsistent rigidity and functional tremor may also be present.

Axial Disorders

Functional disorders of gait and posture are commonly seen in patients with FNDs. Features suggestive of functional gait include excessive gait slowness, noneconomic posture, astasia-abasia, sudden knee buckling, and excessive demonstration of effort, referred to as the "huffing and puffing sign." Functional postural abnormalities include propriospinal myoclonus, involving myoclonic-like jerks affecting the trunk.

Nonepileptic Seizures

Nonepileptic seizures (NESs) are the most common type of FND. Differentiating between NES and epileptic seizures (ESs) can be challenging. One difficulty is that the disorder is paroxysmal, and examination of the patient may well be normal. It is important to see an event, and a family member or friend should be asked to video the event if this has not been done already. Signs that may help to reliably distinguish NES from ES include long duration, fluctuating course, eye closure at onset, eye fluttering, ictal crying, memory recall, and preserved awareness. The presence of pelvic thrusting and asynchronous or side-to-side movements may also be used to reliably distinguish NES from ES, with the caveat that frontal-lobe partial seizures can also present with these signs. Although history-taking in patients with seizures often includes questions about the presence of urinary incontinence and tongue biting, these features do not reliably distinguish between ES and NES.[4]

Speech and Voice Disorders

Functional speech and voice disorders can present in a variety of ways affecting articulation, prosody, or phonation. As with other functional neurologic symptoms, functional speech and voice disorders can be distinguished by their variability, suggestibility, and distractibility. Articulation deficits can present as a dysfluency similar to stuttering; functional stuttering can be differentiated from nonfunctional stuttering by its excessive consistency or excessive variability, or by the presentation of accenting the wrong syllable. Prosodic abnormalities affect the rhythm and intonation of speech and can include foreign accent syndrome or child-like prosody. Patients can also present with aphonia or dysphonia in the absence of vocal cord or neurologic pathology sufficient to account for the severity of their voice disorder.[1]

Sensory Symptoms

Functional sensory symptoms present with alteration of normal sensation in the absence of neurologic disease and are characterized by internal inconsistency. Physical signs suggestive of functional sensory loss include splitting of vibration sense across the forehead or sternum, precise midline splitting of a sensory deficit that ignores the crossover of cutaneous sensory nerves, nonanatomic sensory loss, and inconsistencies in sensory testing. Functional sensory signs must be interpreted with caution, however, given the relatively poor reliability and validity of sensory signs. While splitting of vibration sense and midline splitting have been demonstrated to have a high specificity for FNDs, inconsistencies in sensory testing may also be seen in patients with parietal or thalamic lesions.[1]

Functional visual loss can present with nonphysiologic visual field constriction, also referred to as tubular visual field defect, in which the area of the visual field defect remains unchanged despite changing distances from the visual target. Patients with functional vision loss may report a similar visual acuity at full distance and half-distance from the eye chart. Functional monocular vision loss can also present with a "missing half" defect, in which a complete hemianopia is present when both eyes are open, but a normal visual field is present when the unaffected eye is tested alone.[1]

Functional Dizziness

Dizziness is a common complaint and many patients will have an identifiable abnormality of the vestibular or related systems. Many patients have had some sort of vestibular insult that has resolved, or perhaps only an anxiety attack. They then might develop a complex of symptoms including prolonged episodes of dizziness or unsteadiness that are triggered by an upright posture, motion of any part of the body, or complex visual input. Symptoms may worsen over time and lead to significant distress or functional impairment. The symptoms cannot be explained by the objective findings on examination or by quantitative vestibular testing. This is called persistent postural-perceptual dizziness.

DIAGNOSTIC CRITERIA

Diagnostic clinical criteria for NES have been established by the International League Against Epilepsy. These criteria allow for a laboratory-supported diagnosis of documented NES with high interrater reliability. The gold standard for diagnosis of NES entails recording a typical event or ictus on video electroencephalography, with absence of epileptiform activity during the peri-ictal period, as well as ictal semiology and history consistent with NES.[4]

There are several proposed diagnostic criteria for functional movement disorders. While they vary in their characterization of levels of clinical certainty, all of these diagnostic criteria rely on the presence of the positive signs described earlier. Phenotype-specific diagnostic criteria have been proposed by Espay and Lang, allowing functional movement disorders to be diagnosed with clinically definite certainty exclusively on the basis of a careful neurologic examination performed by a neurologist with expertise in movement disorders. Historic elements and psychiatric comorbidities are not deemed a useful part of the diagnostic process according to these criteria, as both may be misleading.[5] Although many patients with a functional movement disorder can be diagnosed on the basis of a careful examination, there is utility in performing electrophysiologic tests in some patients. The Gupta-Lang criteria accordingly introduced a laboratory-supported diagnostic category, in which electrophysiologic tests confirming the diagnosis of functional tremor or functional myoclonus are used to make a definitive diagnosis of functional movement disorder.[1]

ETIOLOGY

There is no single cause for FNDs. Their etiology appears to be multifactorial, with different components important in different people. Current understanding is based on a bio-psycho-social model, with interactions among biologic, psychologic, and social factors. Among the social factors, one important finding is that there is an increase in early childhood trauma of all types including sexual, physical, and psychologic, in patients with FNDs.[6] Trauma at that time increases stress and circulating cortisol, and increased cortisol can damage the developing brain, leading, for example, to smaller hippocampal size. It has even been shown that emotional stress of the mother during pregnancy can influence brain development. This causes a decreased resilience to stress later in life. Other social factors include contemporary stress related to work or family. Due to decreased resilience, the stress does not need to be exceptional, and, indeed, many patients deny that they have greater stress than others.

As regards psychologic factors, many studies show an increased prevalence of anxiety and depression, especially the former, in patients with FNDs. These are important comorbidities and might share etiologic factors with FND. Biologic abnormalities have also been identified. For example, there are changes in local brain volume and changes in the white matter as shown with diffusion tensor imaging. One study with voxel-based morphometry of patients with functional movement disorders found changes in the left amygdala, left striatum, left cerebellum, left fusiform gyrus, bilateral thalamus, and left sensorimotor cortex.[7] Changes in the amygdala might reflect damage by early life trauma.[8] Other changes seem to reflect involvement of the motor system. There may well be some genetic predisposition as well.[9] In certain psychiatric disorders, epigenetic changes, likely due again to early life trauma, appear partly etiologic, and this might be true also of FNDs. Studies of heart rate variability in a patient group with functional movement disorders showed decreased variability, and such a finding might correlate with decreased resilience to stress.

PATHOPHYSIOLOGY

The pathophysiology refers to the genesis of symptoms.[10] There must be a link from etiology to pathophysiology, but this is not understood at this time. The first observation in all FNDs is that elemental motor and sensory function appears to be normal despite any apparent clinical abnormality. For example, in the motor system, despite apparent weakness, strength can be demonstrated with Hoover sign, and transcranial magnetic stimulation can show a normal pathway from motor cortex to muscle. In the sensory system, patients with functional somatic sensory disorders have normal early somatosensory evoked potentials, and those with functional dizziness will have normal vestibular function. The abnormality is therefore at “higher” levels in the central nervous system. In sensory systems, this could be in association areas or in the downward modulation of primary areas. In the motor system, this could be from influences almost anywhere in the brain, as virtually the entire brain influences the motor system. There is a particularly interesting finding in functional weakness that does implicate top–down processes. Motor evoked potentials (MEPs) produced by transcranial magnetic stimulation are ordinarily enhanced when a subject imagines moving the target muscle. In patients, the MEP decreases in size. There is evidence for overactivity of the limbic system, which might be the main source of the problem. Indirect evidence comes from an exaggeration of the startle reflex, which importantly is modulated by the amygdala. Direct evidence comes from a functional magnetic resonance imaging (fMRI) study of the reaction of the brain to faces that show different emotions. Patients with functional movement disorders showed increased activation of the right amygdala to both happy and fearful faces.

The other aspect of the pathophysiology is the involuntary nature of symptoms. This has been studied in functional movement disorders, and there appears to be an abnormality of the right temporoparietal junction region. This region is a major node in the brain’s processing of the sense of agency, the sense that the person is the “agent” that made the movement. Strong evidence for this abnormality came from an fMRI study looking at patients with functional tremor.[11] The fMRI activation was compared between the functional tremor and a voluntary mimic of the tremor. Decreased activity was found at the right temporoparietal junction when patients exhibited functional tremor. Abnormality of this region was subsequently found even in a resting-state fMRI study.[12] Thus, the abnormal movements seem involuntary to the patient. How this all happens is not clear, but there might be an abnormal feedforward signaling from the movement generation process.

TREATMENT

Delivery of the Diagnosis

Appropriate delivery of the diagnosis is the first step and an important part of the therapeutic process, with early diagnosis and acceptance of the diagnosis serving as predictors of positive outcome.[1] The diagnostic encounter serves multiple objectives. The patient should ideally emerge from this encounter with confidence in their diagnosis, a sense of partnership with their neurologist, and an understanding of the multidisciplinary nature of the subsequent management.

FND, in the majority of cases, is a definitive diagnosis and should be presented in this manner to the patient. Patients should be informed that there is an established diagnosis, using clear language they can readily understand. The rationale behind the diagnosis should also be provided. Just as patients with multiple sclerosis are informed about the results of their brain MRI and lumbar puncture, patients with FNDs should be presented with the evidence supporting their diagnosis. Showing patients with FNDs the features of their neurologic examination that led to their diagnosis is integral in establishing confidence in the diagnosis. Patients with functional tremor can have their attention drawn to the entrainment or suppression of their tremor with contralateral tapping, whereas patients with functional weakness can be shown a positive Hoover sign.[13]

The disorder should be explained in layperson’s terms within the biopsychosocial framework described above. Importantly, the potential for reversibility with treatment should be stressed. Given limited public awareness about FNDs, it is helpful to provide the patient with additional educational resources to review after the consultation. Patients can be directed to online resources such as www.nonepilepticattacks.info and www.neurosymptoms.org, and to patient organizations such as www.fndhope.org.

Developing a sense of trust and partnership between the patient and physician at the time of initial diagnosis is important in the context of the growing recognition of the role of the neurologist as coordinator of care for patients with FNDs. In addition, symptomatology in these patients may evolve over time, and patients should feel comfortable in returning for a re-evaluation should new symptoms arise.

Psychologic Treatment

Psychologic treatment has traditionally been considered the standard of care in the treatment of FNDs. While the literature on evidenced-based treatment of FNDs is scarce, evidence has grown nevertheless for the efficacy of psychologic treatment. One meta-analysis demonstrated a substantial reduction in seizure frequency in over three-quarters of patients with NES treated by psychologic interventions.[14] Various types of therapy have shown promise, including disorder-adapted cognitive behavioral therapy (CBT), multimodal cognitive behavioral-informed psychotherapy, CBT-oriented self-management, and interdisciplinary psychodynamic interpersonal therapy. The overall goals of psychologic treatment are to explore and address unhelpful beliefs and behavior, which may influence symptom control, self-esteem, mood, and anxiety. Patients are taught to identify how their thinking affects their emotional state and their behavior and to identify triggers exacerbating symptoms.[15] Pilot studies have demonstrated significant benefit of CBT in treating a range of functional neurologic symptoms, including functional tremor[16] and NES.[17] In addition to improvement in clinical symptoms, patients with functional tremor exhibited significant changes in activation within the emotion-processing network after a 12-week CBT program, as assessed by fMRI during a basic-emotion processing task.[16]

Motor Rehabilitation

Physical therapy has an important role in the multidisciplinary treatment of patients with prominent motor symptoms. A set of consensus recommendations has identified principles to guide this type of therapy. These recommendations suggest that physical therapy programs can and should work within the biopsychosocial model of functional movement disorders, in which a patient's abnormal movements are involuntary but also represent learned habitual movements driven by abnormal self-directed attention. CBT and stress reduction techniques can be incorporated into the physical therapy to normalize illness beliefs and change maladaptive behaviors. Physical therapy for functional movement disorders focuses on function and automatic movements (e.g., walking) rather than on impairments (e.g., weakness) and controlled movements (e.g., strengthening exercises).[18]

Other Treatment Options

If present, comorbid depression or anxiety may be treated pharmacologically. A variety of nonpharmacologic interventions have also been used, including transcutaneous nerve stimulation, transcranial magnetic stimulation, biofeedback, and therapeutic sedation.[15] Further work is needed to evaluate the efficacy of these interventions.

Multidisciplinary Approach

It is often the case that patients need attention from several disciplines, including psychiatry, physical therapy, and social work. It can be debated who should manage the team, but this can certainly be an appropriate role for the neurologist. Patients with FNDs have neurologic symptoms and neurologists are in an optimal position to make continuing assessments and redirect treatment as necessary.

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SECTION

14

Imaging and Perioperative Care

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CHAPTER

53

Neurologic Complications of Imaging Procedures

WILLIAM P. DILLON ■ MATTHEW R. AMANS

IONIZING RADIATION
COMPLICATIONS OF INTRAVENOUS INJECTION OF CONTRAST MATERIAL
  Iodinated Contrast Media
  Contrast Media for Magnetic Resonance Imaging
  Miscellaneous Complications of Contrast Media
NONINVASIVE IMAGING PROCEDURES
  Computed Tomography
  Magnetic Resonance Imaging
SPINAL PROCEDURES
  Myelography and Intrathecal Injections of Contrast Media
    Terminology
    Technique
    Complications of Intrathecal Puncture
    Complications of C1–C2 Puncture
    Complications from Intrathecal Administration of Contrast Agents
  Discography
  Epidural and Transforaminal Anesthetic Neural Block
ANGIOGRAPHY
  Cerebral and Aortic Angiography
  Spinal Angiography
  Peripheral Angiography
EMBOLIZATION AND STENTING PROCEDURES

Neurologic complications of imaging examinations and image-guided procedures are varied and largely related to excessive or inappropriate use of ionizing radiation-based imaging studies, local complications of the invasive procedure, complications related to exposure to high magnetic fields, or complications arising from the use of intravenous contrast agents. This chapter provides a summary of neurologic complications related to those imaging procedures that are commonly performed in modern radiologic practices. Some historic perspective is presented as well, and the reader must be aware that changes in the practice of radiologic procedures affect the kinds of complications and their incidence over time.

IONIZING RADIATION

The safety of patients and healthcare workers in diagnostic and interventional radiology is based on three fundamental principles of radiation protection of patients: justification for an imaging procedure, optimization of the imaging procedure, and the application of ionizing radiation doses “as low as reasonably achievable” (ALARA).[1]

COMPLICATIONS OF INTRAVENOUS INJECTION OF CONTRAST MATERIAL

Radiographic contrast agents have been in use for over 70 years and are employed in approximately 10 million radiographic procedures annually in the United States. They find wide use in the evaluation of disease processes both within the central nervous system (CNS) and throughout the body. Contrast material helps to define normal vascular anatomy as well as pinpoint patterns of abnormal contrast enhancement indicative of pathologic processes. Most patients tolerate radiographic contrast with few or no side effects.

Iodinated Contrast Media

Iodinated contrast medium is used extensively for intravenous and intra-arterial x-ray imaging examinations.

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The risk of adverse reactions is low, especially as usage has changed from ionic to nonionic, low-osmolality agents. The latter has largely replaced ionic high-osmolality agents and is associated with an incidence of acute adverse reactions (allergic-like plus physiologic) of less than 1 percent. Another advantage of nonionic agents is their isotonicity, which markedly reduces the sensation of heat and flushing.[2]

Contrast reactions are sporadic and largely unpredictable. A prior allergic reaction to contrast material is a substantial risk factor for a recurrent allergic-like adverse event. Atopic individuals and asthmatics are also at increased risk for allergic-like contrast reactions. In addition, hemodynamic changes may occur during or shortly after injections in patients with various cardiovascular diseases.

Idiosyncratic allergic reactions may occur on first or subsequent contrast administration and range from hives to more severe reactions such as pulmonary or cerebral edema, laryngospasm, bronchospasm, and cardiovascular collapse. Dose-related effects of tonicity and chemical toxicity mainly affect the heart, lungs, and kidneys and include cardiovascular depression and renal failure. Life-threatening reactions occur in approximately 0.05 to 0.16 percent with ionic contrast media injections and 0.03 percent with nonionic contrast materials; the death rate, however, is similar with both types of agents, occurring in approximately 1 to 3 per 100,000 injections.[2,3]

Regardless of the type of contrast medium used, extravasation into the soft tissues of the arm at the time of injection may lead to local tissue injury, including skin necrosis. Swelling, which attends severe extravasation injuries, may also lead to compartment syndromes and therefore to injury of peripheral nerves. This is a rare complication, but the risk increases with the use of automated power injectors, and the administration of contrast to infants, young children, and unconscious or debilitated patients (such as diabetics or patients receiving chemotherapy).

Contrast Media for Magnetic Resonance Imaging

Most contrast agents for magnetic resonance imaging (MRI) are variations of chelates of gadolinium, a lanthanide metal. Gadolinium is toxic in its free form, but through chelation with diethylenetriamine penta-acetic acid (DTPA) or other moieties is typically eliminated from the body by renal clearance. Gadolinium-based contrast media are considered safe and well tolerated by the vast majority of patients; the incidence of complications is less than 0.5 percent. Minor side effects including headache, nausea, and vomiting, are sometimes noted, but the risk of immediate hypersensitivity reactions is extremely low, on the order of 1 per several 100,000 injections.[4] Nonetheless, severe immediate hypersensitivity reactions and death secondary to gadolinium administration do occur. Clement and coworkers have shown that, while rare, allergic hypersensitivity reactions are identified in up to 20 percent of patients experiencing a reaction to intravenous contrast material, including gadolinium,[4] and there is a high incidence of cross reactivity with other agents in the same family, especially for gadolinium agents.

Gadolinium agents cross the placenta, with undetermined effects on developing fetuses, and are seen in small amounts in the breast milk of lactating mothers; therefore, they are not recommended for use in pregnant women unless absolutely necessary. It is unlikely that the small amount of gadolinium absorbed by a nursing infant's gastrointestinal tract is harmful but, if concern exists, the nursing mother can be advised to discard her breast milk for 24 hours after gadolinium administration.

Based on the structures of the chelating ligands, gadolinium contrast agents can be divided into two categories: linear and macrocyclic. According to their charges, gadolinium can also be subclassified into ionic or nonionic agents. Macrocyclic and ionic agents are more stable than linear agents, as the free gadolinium is completely isolated within the preformed cage of the macrocyclic chelate whereas, in linear molecules, free gadolinium is wrapped around with elongated ligands. Gadolinium may become disassociated from its chelated agent and is then deposited in the tissues, including the brain. This occurs primarily in the dentate nucleus of the cerebellum, but in other areas as well. No known deleterious effects have been identified from this deposition seen on T1-weighted MR scans as high signal, particularly with repeated injections of linear gadolinium agents.[5]

Nephrogenic systemic fibrosis, characterized by fibrosis of skin and other organs, is a rare disorder caused by deposition of free gadolinium following administration to patients with acute renal failure. For this reason, the use of linear gadolinium agents is not advised in patients with a glomerular filtration rate of less than 30 mL/min per 1.73 m^2. Macrocyclic gadolinium contrast agents are much less likely to cause this complication and can be safely administered to patients with glomerular filtration rates between 15 and 30 mL/min per 1.73 m^2.

Other novel MRI contrast agents are now available for limited clinical applications. The superparamagnetic iron chelates work on the basis of reducing signal within normal tissues such as lymph nodes and liver and thus provide contrast for nonenhancing abnormal tissues. Chelates of manganese are also approved for liver imaging. Free manganese has a theoretical risk of parkinsonian complications, but the chelated compound caused no serious side effects during phase 2 clinical trials. Intravascular contrast agents are being evaluated and promise to improve magnetic resonance angiography and perfusion of brain tumors.

Deleterious effects of MRI exposure on pregnant women or the developing fetus have not been shown. Nevertheless, it is recommended that women of reproductive age be screened for pregnancy before entering the MR environment. The clinician should confer with the radiologist and document that the information cannot be acquired by other nonionizing means (e.g., ultrasonography), that the information is needed to care for the patient or fetus during the pregnancy, and that it is not prudent to wait until the patient delivers to obtain the scan.

Miscellaneous Complications of Contrast Media

Rare complications of contrast administration include retrograde reflux of contrast material via the abdominal port of a ventriculoperitoneal shunt after bladder rupture sustained during voiding cystourethrography. The extravasated contrast medium then tracked up the ventriculoperitoneal shunt, causing seizures and ventriculitis. Venous air embolism has been documented during infusion of contrast medium, due to either scalp vein malposition or inadvertent trapping of air within power injectors or tubing. Venous air embolism can cause a stroke, especially in infants with patent cardiac foramen ovale or other right-to-left shunts.

Acetazolamide, a vasodilator of the cerebral circulation, is now occasionally administered for perfusion MR or computed tomography (CT) studies. Comparison of studies before and after acetazolamide allows determination of the cerebral vascular reserve. Acetazolamide, although well tolerated, has minor side effects such as nausea and headache. It is a diuretic, so adequate hydration and satisfactory serum potassium levels must be ensured, particularly in those already receiving diuretics for medical reasons. Acetazolamide is probably not indicated in the setting of acute stroke because its diuretic effect may reduce cerebral perfusion.

NONINVASIVE IMAGING PROCEDURES

Computed Tomography

Neurologic complications of x-ray CT are related to complications of sedation, contrast administration, or other mishaps that incidentally attend the procedure. There is a small risk of radiation-induced cataracts, leukemia, and other tumors following multiple CT studies, especially in children. This concern has increased with recent technologic advances: helical-mode scanners are now used routinely in CT angiography and CT perfusion studies to scan rapidly large regions of the body. Multiple scans during infusions of contrast material may result in additional radiation exposure. For this reason, MRI and ultrasound are better methods for following patients who require repeated imaging procedures, as long as their diagnostic benefit is equivalent to or better than that of CT.

Magnetic Resonance Imaging

MRI has rapidly gained wide acceptance in the imaging of the CNS as well as for musculoskeletal and many cardiac and general body applications. Images are produced by placing a patient in an extremely strong static magnetic field (on the order of 15,000 to 30,000 times the Earth's magnetic field) and then probing the magnetic relaxation properties of water protons in the body using radiofrequency pulses; computer mathematical manipulation allows the production of images.

Because of the need for a very strong, continuous magnetic field, the presence of metal objects near the imaging environment can be hazardous, since they can accelerate toward the magnet, acting as missiles with resultant harm to patients and staff. Anyone coming into proximity of an MRI machine is therefore routinely screened for ferromagnetic objects prior to entering the magnet room. The major contraindications to MRI examinations include the prior placement of ferromagnetic aneurysm clips or cardiac pacemakers, intraocular metallic foreign bodies, certain types of prosthetic cardiac valves, electronic or magnetically activated medical devices, and any other large, potentially ferromagnetic foreign body. Pacemakers have long been considered an absolute contraindication to MRI, but recent literature suggests that these studies can be safely performed in some patients as long as precautions are taken before, during, and after the study and the benefit of MRI outweighs the risk of pacemaker malfunction or harm to the patient. Implanted cardiac defibrillators likewise have led to no adverse events from repetitive MRI at 1.5 T in patients with implanted defibrillators.

The hazard of aneurysm clips deserves special attention. Most currently manufactured aneurysm clips have few if any ferromagnetic properties, as judged by lack of deflection within a magnetic field when tested in vitro. At least one instance of fatal clip movement in a patient has, however, been reported, and in that case was due to inaccurate information supplied during the screening process. Newer nonferromagnetic clips, such as titanium alloys, are safe at 1.5 T, but discretion is always advised. At higher field strengths, such as 3 T, titanium alloy clips are preferred if MRI is necessary, but care must be taken while moving patients through the opening of the bore toward the center of the magnet, as the largest torque forces occur during this maneuver. The potential information to be gained from the procedure must be carefully balanced against the potential danger of clip movement. Although the metal from the clip may cause significant artifact on the examination, useful information can often still be gleaned by appropriately tailoring the examination.

The potential risks of metallic stents and endovascular detachable coils also merit consideration. A new generation of MRI scanners, including at 3.0 T, with shorter lengths and wider apertures (e.g., 70 cm diameter and about 160 cm length), results in much larger gradients. Larger magnetic susceptibility of the employed material, larger mass, higher magnetic field, and larger gradient will increase the magnetic force on the metallic implant upon entering the MRI magnet. These devices produce ferromagnetic artifacts, and thus the local anatomy is distorted on MRI. MRI is safe at 1.5 T for patients who have recently had placement of a coronary stent.

Some monitoring devices are potentially dangerous because looped metallic wires may acquire induced currents, resulting in burns to the skin attachment sites. The US Food and Drug Administration (FDA) received 1,568 adverse event reports for MR systems between January 1, 2008 and December 31, 2017. Thermal events were the most commonly reported serious injury (59%). In addition, mechanical events—defined as slips, falls, crush injuries, broken bones, and cuts; and musculoskeletal injuries from lifting or movement of the device—were observed in 11 percent, projectile events in 9 percent, and acoustic events in 6 percent.[6] For this reason, all physiologic monitoring equipment and other devices must be carefully screened and approved specifically for use during MRI. Exposure of electrically conductive leads or wires to the RF transmitted power during MR scanning should be performed with caution and appropriate steps taken to ensure that lead or tissue heating does not result. Patients who require EKG monitoring and who are unconscious, sedated, or anesthetized should be examined after each MR imaging sequence and repositioning of the EKG leads and any other electrically conductive material with which the patient is in contact should be considered. Extensive testing and safety information about specific devices is available from MRIsafety.com as well as from Shellock and associates.[7]

Screening of patients referred for MRI is essential prior to the examination. If patients are unable to fill out a questionnaire or are unconscious and their family is not present or unable to provide the required information, they should be thoroughly examined by medical personnel with attention to surgical scars. If these are present, a radiograph is suggested prior to MRI. When in doubt, the presence of a specific medical device must be documented precisely and in writing before entry of the patient into the magnet. This information can be checked against the known magnetic deflection properties of the device, as appropriate. In patients with a history of possible metallic ocular foreign body, plain radiography of the orbit or low-dose orbital CT can be used to exclude the presence of significant metal fragments, as these can move in the magnetic field and result in ocular injury and blindness.

Another potential hazard related to the static magnetic field required for MRI is that of missile injury, mentioned earlier. The missile effect is perhaps the most serious potential hazard because many clinicians entering the MR environment are not aware that the magnet is always "on." Paper clips, scissors, vacuum cleaners, chairs, floor buffers, oxygen tanks, anesthetic equipment, and other ferromagnetic metallic items have been pulled rapidly into the bore of a magnet when inappropriately brought close to it, sometimes with fatal results. Proper introduction to safety precautions for visitors is important. The American College of Radiology recommends that zones of access be created and labeled to inform the public as they get closer to the magnet room itself.

The rapid switching of the gradient coils used in MRI may result in induced voltage and current in implanted wires, such as cardiac leads or brain-implanted electrodes, as well as thermal injuries. MRI gradients may cause a loud vibration or banging noise that can result in hyperacusis or tinnitus. Both temporary and permanent instances of hearing loss have also been reported; for these reasons, the use of earplugs is mandatory during

MR examination for all patients as well as accompanying parents or visitors within the magnet room. These are especially recommended in cases requiring very rapid switching of gradient coils, as with most MR angiography sequences and ultrafast techniques such as fast spin-echo and echo-planar techniques (e.g., diffusion and perfusion imaging and functional MRI). Tissue heating is also a potential but relatively insignificant complication of MRI. The FDA limits the specific absorption rate, which is the radiofrequency energy deposition, to 0.4 W/kg averaged over the body. In animal studies, levels at 10 times this rate over a 75-minute period raise the skin and eye temperature of a sheep by only 1.5°C, with no observed side effects. Nonetheless, the FDA has determined limits, particularly for small infants and children.

SPINAL PROCEDURES

Myelography and Intrathecal Injections of Contrast Media

The number of myelographic procedures has diminished dramatically since the introduction of MRI and CT. MRI is superior to myelography in the evaluation of lumbar disc disease, discitis and vertebral osteomyelitis, myelopathy, and extradural and intradural spinal mass lesions.

When myelography is recommended, it usually is performed in conjunction with CT. CT myelography is preferred to plain-film myelography for evaluating the thecal sac in those patients who cannot tolerate MRI because of severe claustrophobia or because of other contraindications to the magnetic environment, discussed previously. Many patients with severe spondylitic disease of the spine or failed-back syndrome may benefit from CT myelography. In such instances, a lumbar puncture is performed for instillation of 5 to 8 ml of iodinated nonionic contrast before thin-section CT scanning is performed. In many patients, CT myelography may complement MRI, especially in patients who have bony osteophytes that may be difficult to distinguish on MR or in those with metal implants that obscure MR images.

Few indications remain for traditional plain-film (high-dose) myelography. Those with suspected cerebrospinal fluid (CSF) loculations or arachnoid cysts may still benefit from myelography because the septations separating these CSF-filled structures can be difficult to detect on MRI and the dynamic nature of myelography can be useful. In addition, myelography in combination with CT is required occasionally to locate precisely the site of a spinal CSF leak. Conventional myelography is also indicated occasionally for the evaluation of patients with back pain after orthopedic instrumentation because CT and MRI are often compromised by metallic artifacts.

The reduction in myelograms performed at teaching institutions has reduced the exposure of trainees in radiology to this procedure. As with any procedure, the incidence of complications associated with a procedure relates to the experience of the practitioner. In the case of myelography, it is our impression that the rate of complications is on the rise because of the decrease in experience of recent trainees. It is therefore appropriate to review the neurologic complications of myelography and intrathecal injections of contrast material despite their decline in use.

TERMINOLOGY

Myelography entails plain-film examination of the spine following intrathecal instillation of iodinated contrast media through either a lumbar puncture or a cervical puncture at the C1–C2 level, posterior to the spinal cord. Water-soluble, nonionic contrast agents are used exclusively. Using a tilt-table and fluoroscopy, the contrast is positioned by gravity into the area of interest. Cervical, thoracic, and lumbar myelography as well as “total” myelography can be accomplished through a single needle puncture. Before MRI, the choice of a lumbar or C1–C2 puncture was largely determined on the basis of clinical symptomatology. Low-dose (lower than routinely administered for plain-film myelography) injections before CT scanning, so-called *CT myelography*, has replaced formal plain-film myelography. Current multidetector high-speed CT scanners are capable of high-resolution, less than 1-mm contiguous scans through the entire spinal canal in less than 30 seconds and, from these, superb tomographic reformations in the sagittal and coronal planes are possible. Occasionally contrast must be positioned intracranially to opacify the CSF cisterns. MRI has now largely replaced CT cisternography, but it is still used occasionally to evaluate for CSF leak and the presence of intracranial arachnoid cyst.

TECHNIQUE

Several approaches are used to perform intrathecal injections. Typically, a 22-gauge or smaller spinal needle is positioned with fluoroscopic or CT guidance in the lumbar subarachnoid space. This requires topical and subcutaneous anesthesia and is contraindicated in those with bleeding disorders. While lateral fluoroscopy was for many years the preferred technique for C1–C2 puncture, the puncture is performed more safely using CT guidance so that the needle can be placed posterior to the spinal cord. C1–C2 puncture carries a risk of cervical cord puncture, and efforts must be taken to avoid this by proper positioning of the patient and careful technique. Alternatively, low-dose injection of contrast medium via the lumbar route is adequate to examine the cervical spine and is associated with fewer potential complications than the C1–C2 route. CT is performed immediately after instillation of contrast medium. Delayed CT was used in the past to evaluate for syringomyelia, but MRI now best evaluates this condition.

Cisternal puncture in the suboccipital region is rarely if ever performed. The authors have never performed this procedure themselves and see little indication for its use in the current era of MRI.

COMPLICATIONS OF INTRATHECAL PUNCTURE

The neurologic complications of myelography and intrathecal injections can be separated according to those related to intrathecal needle puncture itself and those related to the administration of intrathecal contrast material.

Vasovagal Response

Vasovagal syncope occurs infrequently during lumbar puncture. Its occurrence can be anticipated by communication with the patient and by noting the initial appearance of diaphoresis. This usually occurs during head elevation and can be countered by prompt lowering of the patient's head.

Headache

Headache and associated nausea and vomiting are the most frequent complications of lumbar puncture and myelography. The incidence of headache after myelography decreased with the development of nonionic, water-soluble contrast agents. The etiology of the headache is often obscure and may be related to neurotoxic effects of the contrast agent, persistent CSF leak at the puncture site, or psychologic factors. The incidence of postdural puncture headache can be reduced by the use of a small-gauge lumbar-puncture needle. Other factors that have been identified include sex (11.1% female vs. 3.6% male), age (11.0% 31 to 50 years of age vs. 4.2% others), previous history of postpuncture headache (26.4% positive vs. 6.2% negative), and needle bevel orientation (16.1% perpendicular vs 5.7% parallel to the spinal axis). The latency between lumbar puncture and headache onset ranges from 6 to 72 hours and the duration from 3 to 15 days. In 34 of 48 (71%) patients with postlumbar puncture headache, at least one of the following was present: neck stiffness, tinnitus, hypoacusis, photophobia, or nausea. The condition is usually self-limiting; caffeine alleviates the symptoms and reduces the course of the illness. When bed rest and caffeine prove ineffective, an autologous epidural blood patch at the site of puncture works well for the majority of patients.

After myelography, it is common practice to keep patients in a supine position, with the head elevated approximately 25 to 45 degrees. Short-duration (1 hour) is as effective as long-duration (4 hours) supine recumbency in preventing postlumbar puncture headache. Oral hydration is also encouraged.

Hearing Loss

Hearing loss has been described as an adverse reaction after lumbar puncture as well as after myelography. It may be uni- or bilateral, and transient or permanent. Alteration in the pressure equilibrium between CSF and perilymph in the setting of a patent cochlear aqueduct may result in the release of perilymphatic fluid into the subarachnoid space; alternatively, a direct toxic effect of contrast material on the inner ear may be a factor in hearing loss. The use of small-gauge spinal needles has been recommended to reduce the leakage of CSF through the dural puncture. The use of nonionic myelographic agents is now standard, and these agents have been shown to be safer than ionic formulations.

Epidermoid Tumors

Iatrogenic intraspinal epidermoid tumors have been reported as sequelae of lumbar puncture. It is believed that implantation of epithelial cells from the skin into the thecal sac or the epidural space during lumbar puncture may allow this benign tumor to grow gradually. The incidence of iatrogenic epidermoid tumors is exceedingly rare, but up to 40 percent of those occurring in the lumbar spine are thought to relate to prior lumbar puncture. The time from lumbar puncture to tumor presentation is typically from 2 to 8 years. Epidermoid tumors appear on MRI as masses with signal characteristics similar to CSF, but with reduced apparent diffusion coefficient derived from diffusion-weighted images. The presence of this rare tumor should arouse suspicion of possible iatrogenic causes, and a history of prior lumbar puncture should be sought.

Hemorrhage

Intracranial hemorrhage secondary to myelography has been well documented. It is likely that this complication relates to persistent CSF leakage and low intracranial CSF volume, which then result in the production of subdural hematomas or intracranial hemorrhages. Direct laceration of a vessel is rare. Acute epidural hematoma complicating myelography in a normotensive patient with normal blood coagulability is rare but has been reported.

Spinal punctures should not be performed in the setting of abnormal coagulation factors. In patients receiving systemic anticoagulants, there is an increased risk of epidural hematoma at the site of puncture. The Society of Interventional Radiology published consensus guidelines in 2019 for the management of coagulation status prior to image-guided procedures.[8] It recommends that prior to spinal procedures such as lumbar puncture, vertebroplasty, and nerve blocks or epidural injections, an INR above 1.5 and platelet count below 40,000/μL should be corrected, and that clopidogrel (Plavix) should be stopped for 5 days and low-molecular-weight heparin for 1 day prior to the procedure.

Puncture of the Spinal Cord

Although uncommon, puncture of the spinal cord has been described during lumbar puncture. This complication can be avoided by restricting lumbar punctures to below the L2 level. A low-lying conus or tethered cord will increase the risk of cord puncture, and it is therefore important to review the MR or other spinal imaging studies prior to lumbar puncture.

COMPLICATIONS OF C1–C2 PUNCTURE

Complications related to the C1–C2 approach have been well documented in the literature and include direct puncture of the spinal cord, laceration of epidural and vertebral venous and arterial structures, and spinal cord compression related to neck hyperextension during the procedure. Spinal cord and blood vessel punctures are the most serious complications and occur during fluoroscopic-guided procedures primarily because of incorrect positioning of the patient's neck and misdirection of the x-ray beam.

The indications for C1–C2 puncture are infrequent. In those patients who cannot undergo MRI but who require cervical myelography, low-dose CT myelography through a lumbar puncture often suffices. This route of administration has been associated with a slightly higher incidence of headache, nausea, and vomiting than with the C1–C2 puncture; however, the use of low-dose, nonionic, water-soluble agents has reduced these complications to an acceptable level. Rarely, a patient who cannot undergo MRI may require C1–C2 puncture to determine the upper margin of a spinal block or a CSF leak in the cervical-thoracic junction.

The injection of contrast material into the spinal cord may be associated with hemorrhagic necrosis of the gray matter and acute neurologic decline. Acute and permanent trigeminal dysesthesias and quadriparesis are reported complications of spinal cord injection. These may be ameliorated by prompt administration of high-dose corticosteroids.

Injection into the epidural venous plexus and intra-arterial injection into an aberrant vertebral artery have also been documented. In approximately 2 percent of patients, the vertebral artery swings inferiorly into the posterior C1–C2 interspace; in such cases, an approach by lateral C1–C2 puncture may then inadvertently lacerate or puncture it. Death of a patient after C1–C2 myelography due to acute subdural hemorrhage as a consequence of laceration of an anomalous intraspinal vertebral artery has been described.

The majority of complications can be attributed to cervical spine hyperextension during the procedure and the remainder to direct complications of the C1–C2 puncture. The narrow sagittal diameter of the spinal canal and severe cervical spondylosis are factors that contribute to hyperextension injury of the cervical spinal cord during prone C1–C2 puncture. Should cervical CT myelography be required, it is our recommendation that it be performed if possible via a low-dose lumbar injection followed by thin-section CT rather than C1–C2 puncture.

COMPLICATIONS FROM INTRATHECAL ADMINISTRATION OF CONTRAST AGENTS

Neurologic complications related to the intrathecal administration of contrast agents range from aseptic meningitis to encephalopathy and seizures. Other reported complications include hyperthermia, hallucinations, depression and anxiety states, and headache. The development of nonionic, water-soluble contrast agents has reduced these neurotoxic side effects significantly. On occasion, intrathecal gadolinium has been used to perform MR myelography in search of a CSF leak. A small amount (<0.3 ml) of gadolinium is administered intrathecally and MR scans are performed following this with fat-suppressed T1-weighted images. An inadvertent overdose of intrathecal gadolinium reportedly has resulted in transient neurotoxic manifestations, including a decreased level of consciousness, global aphasia, rigidity, and visual disturbance.

Meningitis

Both aseptic and bacterial meningitis are reported complications of lumbar puncture and myelography. Bacterial meningitis, which is characterized by the abrupt onset of fever, usually within 24 hours after the intrathecal instillation of contrast, must always be excluded when it is a clinical possibility. Use of facemasks by physicians performing lumbar puncture has been advocated to reduce the possibility of oral contamination. In aseptic meningitis, transient CSF pleocytosis (neutrophils and lymphocytes) and elevated protein concentrations accompany symptoms and signs that are similar to those of bacterial meningitis. Once a bacterial infection has been excluded, the use of corticosteroids may be helpful in relieving symptoms of aseptic meningitis. Persistent leakage of CSF at the puncture site must also be considered in patients with postural headache and pleocytosis, since the clinical picture may be confused with aseptic meningitis.

Seizures

Intrathecal contrast material may cause other, less frequent but potentially serious complications. Encephalopathy, seizures, and focal neurologic deficits have all been reported after myelography, presumably owing to reflux of contrast material into the subarachnoid space about the brain. The risk of seizures is on the order of 0.1 to 0.3 percent with the nonionic, water-soluble contrast agent iopamidol. Increased risk of seizures is present when the total dose of iodine is greater than 4,500 mg, there is a pre-existing seizure disorder, a cervical route of injection is chosen, or the patient is concurrently taking a drug known to lower the seizure threshold.

Inadvertent administration of ionic contrast media used for urography or angiography during myelography causes convulsions that probably arise within the spinal cord itself as well as the brain. These water-soluble, ionic contrast agents are visually indistinguishable from the nonionic contrasts used for myelography; therefore, care must be taken in identifying by their label those indicated for myelography.

Arachnoiditis

Arachnoiditis, or inflammation of the leptomeninges, has also been ascribed to the use of contrast agents for myelography. Iophendylate (Pantopaque), an oil-soluble contrast agent no longer used in clinical practice, was first noted to cause arachnoiditis, especially when accompanied by subarachnoid blood (i.e., after a traumatic tap). Water-soluble contrast agents reduced the incidence of arachnoiditis and were proven safe in the setting of subarachnoid hemorrhage. In many cases it is difficult to ascribe this syndrome with confidence to the contrast agent because confounding variables such as trauma, surgery, infection, or bleeding may have occurred within the spinal subarachnoid space and these have also been associated with arachnoiditis. The issue is further complicated by the observation that arachnoiditis can be induced by intrathecal corticosteroid injections. Clinically, patients usually have symptoms of constant low back pain aggravated by movement. Evidence of multifocal radiculopathy is found on examination. On repeat myelography or MRI, the nerve roots of the cauda equina appear thickened, clumped, and adherent to the periphery of the thecal sac. Enhancement of the roots may occur following intravenous contrast administration. Arachnoiditis is now rarely seen with the use of water-soluble, nonionic contrast agents.

Discography

The value of discography is unclear. The procedure has been advocated in the past primarily as a provocative test that attempts to recreate the patient's back pain syndrome, with the goal of isolating the generator of pain. A needle is placed in the nucleus pulposus of a lumbar or cervical disc and water-soluble contrast agent is injected while observing the patient's response. CT can be performed after discography for added spatial resolution. Although the MRI findings and discography correlate in many instances, MRI does not reliably predict which disc is the cause of a patient's pain.

Discography is a controversial procedure. Carragee and associates found that discography resulted in accelerated disc degeneration, disc herniation, loss of disc height and signal, and the development of reactive endplate changes compared to matched controls.[9]

Complications of discography are related mainly to septic or aseptic discitis. Antibiotics are often added to the contrast media used for discography, but evidence of benefit for their routine use is lacking. Care must be taken to prevent intrathecal instillation of antibiotic-contrast solutions. The incidence of discitis may be related to the length of the procedure, the use of a single needle rather than coaxial technique, and breaks in sterile technique.

Epidural and Transforaminal Anesthetic Neural Block

Patients with back or neck pain often benefit from local anesthetic blockade either to confirm the location of the pain generator or to reduce pain, or both. Diagnostic and therapeutic nerve root blocks involve the local injection of anesthetics (e.g., 0.75% bupivacaine or 1% lidocaine) with or without steroid compounds around exiting nerves or into the epidural space of patients suffering from local or radicular back or neck pain. Injections are administered via a 22- to 25-gauge needle placed into the area of interest using fluoroscopic or CT guidance. Direct injections are made into the epidural compartment of the spine, facet joints, or focally around an exiting nerve near the neural foramen. Complications of these procedures include spinal cord or cerebellar infarction secondary to injection into or spasm of the vertebral or radiculomedullary arteries, inadvertent injection into the spinal cord or nerve root itself, infection, and rare allergic or other side effects related to the injected agents. Botwin and co-workers reviewed the incidence of complications of fluoroscopically guided lumbar epidural injections in 207 patients and found a 9.6 percent incidence of minor complications ranging from transient headache, back pain, leg pain, facial flushing, vasovagal reaction, and increased blood glucose levels, most likely induced by systemic absorption of corticosteroid.[10] Serious complications such as epidural hematoma, spinal cord injection, and paraplegia or quadriplegia secondary to inadvertent injection into the spinal or vertebral artery have been reported following transforaminal epidural nerve block. An outbreak of fungal meningitis caused by contaminated steroid mixtures occurred in 2012.

ANGIOGRAPHY

Angiography is essential in the diagnostic evaluation of many patients with vascular disease, but it carries the greatest risk of morbidity among diagnostic imaging procedures. This risk is generated by the necessity of inserting a catheter into a blood vessel, directing the catheter to the required location, injecting contrast material to visualize the vessel, and removing the catheter while maintaining hemostasis. Skill, experience, and judgment are elements that help reduce the risk of this invasive procedure, but risk cannot be eliminated completely. Moreover, therapeutic transcatheter procedures (embolizations) have become important definitive and adjunctive therapies in patients with cerebrovascular, visceral, and peripheral vascular disease. The decision to undertake a diagnostic or therapeutic angiographic procedure requires sober assessment of the goals of the investigation and its risks.

Neurologic complications of angiography or embolization are the most feared because of the relative permanence of the deficit, which can profoundly impair the patient. Neurologic sequelae are encountered most often in angiographic procedures undertaken to evaluate or treat the vessels of the brain and spinal cord, but they can result from procedures undertaken to evaluate vascular disease elsewhere.

Cerebral and Aortic Angiography

Most aortic arch, carotid, and vertebral arteriograms are carried out by transfemoral arterial access. A common femoral arterial puncture provides retrograde access through the aorta to the aortic arch and great vessels. Selective catheterization of the carotid or vertebral arteries can be accomplished with a wide variety of catheter–guide wire combinations.

While minor complications such as hematoma at the site of vascular access are more common, the most feared complication of cerebral angiography is stroke (Table 53-1). Thrombus can form on or inside the tip of the catheter, especially if the catheter is not flushed properly with heparinized saline at regular intervals. Atherosclerotic intimal plaque may be present along the arterial wall, especially at the common carotid bifurcation. This thrombus or plaque can embolize distally into the cerebral circulation by force of injection or from dislodgment of plaque by the catheter or guide wire. The duration and extent of the resulting ischemic neurologic deficit depend on the size and length of the embolus, its composition (fresh thrombus is thought to fragment more readily), its location, and the available collateral circulation. Identified risk factors for ischemic complications include lack of experience on the part of the angiographer, atherosclerosis, vasospasm, low cardiac output, decreased oxygen-carrying capacity, duration of the procedure, and advanced age.[11] The risk of a neurologic complication has been estimated by many authors and is variable,

TABLE 53-1 ■ Summary of the Most Common Major Complications of Cerebral Angiography

Complication	Rate (%)
Access related	
Hematoma	0.5–1.7
Pseudoaneurysm/AVF	0.04–0.1
Vascular occlusion	0.14–0.76
Infection	0–1
TIA	1.2–2.5
Ischemic stroke	0.1–1
Systemic complications	
Severe allergic reaction to contrast	0.05–0.1
Renal failure	0–0.15
Conscious sedation–related	1.7
Death	0.06–0.1

AVF, arteriovenous fistula; TIA, transient ischemic attack.
Adapted from Alakbarzade V, Pereira AC: Cerebral catheter angiography and its complications. Pract Neurol 18:393, 2018.

but the risk of permanent neurologic deficit is probably between 0.1 and 1 percent depending on the previously mentioned cofactors.[12] A prospective evaluation of 2,899 consecutive angiograms performed by Willinsky and colleagues estimated the risk of neurologic complications to be 1.3 percent, but the vast majority were reversible; permanent ischemic stroke rate was only 0.5 percent.[11]

After cerebral angiography, clinically symptomatic infarcts are rare, but clinically silent infarction as assessed by diffusion-weighted MRI is far more frequent. Among 100 consecutive patients evaluated by Bendszus and colleagues, 23 developed a new lesion on diffusion-weighted imaging after cerebral angiography or embolization.[13] The frequency of lesions was significantly higher in patients with a history of vasculopathy or with vessels difficult to probe. Fluoroscopy time, amount of contrast used, and use of additional catheters were also correlated with the appearance of lesions.

Ischemic complications can also result from intimal dissection of the carotid or vertebral artery by direct trauma from the tip of the catheter or guide wire, allowing thrombus to form underneath a dissected intima and increasing the possibility of a thromboembolic complication. Catheter-induced spasm of an artery also raises the potential for neurologic complications. Although usually temporary, this phenomenon can result in a transient deficit if the spasm prevents adequate blood flow distally, or if a dissection results from further contrast injections within a spastic arterial segment.

Intravascular contrast material injected into the cerebral vasculature may have a hypoxic effect on the brain. In particular, patients with dolichoectasia of the basilar artery may sustain reversible brainstem dysfunction and acute short-term memory loss after multiple contrast injections into the vertebrobasilar system due to reduced contrast washout in the enlarged vessel. Limiting angiographic studies and, if required, the amount of contrast reduces the occurrence of this phenomenon.

Rarely, an intracranial aneurysm ruptures during an angiographic contrast injection, causing subarachnoid hemorrhage. This is reported to result from the force of the injection, although this theory is not accepted universally.

Before catheter insertion into the common femoral artery, the local soft tissues must be infiltrated with an anesthetic agent, usually lidocaine. If the anesthetic agent is inadvertently injected into the femoral nerve, transient dysesthesias may occur along the course of the nerve, which lies medial to the common femoral artery in the inguinal space.

In decades past, common practice dictated the use of a direct carotid artery puncture for the performance of cerebral angiography. Although this technique is now outmoded, rare circumstances might require its use. Administration of a local anesthetic for such a procedure may result in direct intracarotid injection of lidocaine, which can cause generalized seizures. Moreover, intimal damage may occur at the puncture site from the puncture needle or from subintimal contrast or saline injection, the most common cause of a neurologic deficit occurring during direct carotid angiography. Poor hemostatic control of the carotid puncture site may cause an expanding hematoma. Radial artery access is associated with lower bleeding and vascular complications than transfemoral access for patients with acute coronary syndrome, and has become a potential access pathway for cerebral angiography.

Spinal Angiography

Spinal angiography may be indicated to evaluate vascular malformations, fistulas, and tumors and to identify the artery of Adamkiewicz before aortic aneurysm repair. Although the procedure requires the use of relatively large volumes of contrast and is tedious and lengthy compared with most other angiographic procedures, the incidence of complications is low. Chen and Gailloud retrospectively reviewed 302 consecutive spinal angiograms and found no neurologic complications, and an access-related complication rate similar to cerebral angiography of 1 percent.[14]

Peripheral Angiography

Peripheral (noncerebral-noncardiac) angiography also uses a transfemoral approach where possible. Although the cerebral vasculature is not examined per se, there is a risk of producing a cerebral embolic event if the subclavian or axillary arteries require examination because of the adjacent origins of the vertebral and carotid arteries.

Many patients undergo peripheral angiography to evaluate atherosclerotic disease of the abdominal aorta and iliofemoral system, which itself may preclude the use of a femoral artery puncture. If transfemoral access is not possible because of severe atherosclerosis, the axillary or brachial routes may be used. Each has its own set of risks. An axillary puncture is performed with the arm abducted. The axillary artery is palpated, and the puncture is made as deep into the axilla as possible. The left axilla is chosen for most examinations of the descending aorta and its branches; the right axilla is preferred for studies of the carotid and vertebral arteries. For peripheral angiography, an axillary approach carries a twofold to fourfold greater risk of neurologic complications than a transfemoral approach. Stroke can result from dislodgement of atherosclerotic plaque at the origin of the vertebral artery during catheter passage to the aorta. Hemostasis at the puncture site is a much more crucial issue than with a femoral puncture: the axillary artery is more difficult to compress after removal of the catheter, and an expanding hematoma may injure the brachial plexus or its branches. The rate of infection related to catheterization is quite small (see Table 53-1).

Brachial artery access requires the use of a smaller-diameter catheter because of the smaller size of the artery. Risks of cerebral thromboemboli exist as with the transaxillary route. The median nerve can be damaged by needle puncture or by compression from a developing hematoma. Radial artery access may mitigate these risks, but the smaller size of the radial artery requires the use of smaller-caliber catheters.

EMBOLIZATION AND STENTING PROCEDURES

The development of new materials and techniques has advanced the field of interventional neuroradiology, providing in many cases the standard-of-care therapeutic option for patients with difficult and dangerous neurovascular problems. A variety of procedures is available to treat ischemic and hemorrhagic stroke. Stent-assisted percutanous catheter embolectomy has become the primary treatment of acute ischemic stroke, providing a very effective treatment, with a number needed to treat to reduce disability for one patient of 2.6.[15] In addition to being the primary treatment for ischemic stroke within 24 hours of symptom onset, endovascular embolization techniques have become the primary treatment method for most ruptured and unruptured cerebral aneurysms, dural arteriovenous fistulas (DAVFs), vein of Galen malformations, and cerebral vasospasm. For arteriovenous malformations (AVMs), embolization is typically used as a preoperative adjunct to improve surgical outcomes. Intracranial and cervical vascular stenoses are treated with endovascular stenting in select cases, and catheter chemotherapy infusions may be a useful adjunctive tool to surgery in cases of specific tumors in the head and neck and retinoblastoma. Many of these diseases place the patient at high risk of cerebral hemorrhage, stroke, or death. These endovascular treatments have their own risks, and therapy should be tailored to the disease risk of individual patients.

The highest complication rates are found predictably with therapies geared to treating the highest-risk diseases. Among potential complications of endovascular aneurysm therapy are aneurysmal rupture and stroke from thromboemboli. The advent of the electrolytically detachable coil reduced these rates compared to prior balloon techniques. Several studies have evaluated the risks of surgery compared to endovascular coiling. The International Subarachnoid Aneurysm Trial compared outcomes after endovascular and surgical therapy for ruptured aneurysms, and demonstrated a benefit for endovascular therapy at 1 year and 10 years. The patients treated with coil embolization had a slightly higher incidence of rebleeding, but the risk was small and the probability of disease-free survival was much greater than in patients treated by open neurosurgical clipping (OR 1.35).[16]

Endovascular treatment of AVMs is frequently used as a preoperative adjunct to surgical resection or stereotactic radiosurgery. The advent of ethyl vinyl alcohol copolymer has expanded the number of embolizations being performed for AVMs. Other available embolic materials include liquid adhesives such as *n*-butyl cyanoacrylic acid, polyvinyl alcohol particles, and coils. The two most common risks of embolization of AVMs include intracerebral hemorrhage from AVM rupture or vessel wall injury, and stroke from inadvertent embolization of normal arteries or from catheterization. In several studies using different embolic agents (liquid adhesives and polyvinyl alcohol particles) for AVM embolization, the risk of postprocedure neurologic deficit was approximately 8 percent. In many instances, however, deficits were transient and the rate of persistent neurologic deficit was approximately 1.3 percent.[17]

Endovascular therapy is also applicable to vascular problems involving the spinal cord. In the treatment of intramedullary spinal AVMs, which often present with hemorrhage, embolization may provide definitive, palliative, or adjunctive therapy. The major risk is occlusion of normal spinal arteries with embolic material. The spinal DAVF represents a shunt between a dural artery on the nerve root sleeve and an adjacent radicular vein that drains toward the spinal cord, resulting in a venous engorgement syndrome. The risk involved in endovascular treatment of this dural process is lower than when a radiculomedullary artery, which supplies the spinal cord, is involved.

Stents are increasingly used to treat diseases of the supra-aortic vessels. Carotid stenting has been evaluated in comparison to carotid endarterectomy within several clinical trials, with improved results in patients with prior carotid endarterectomy, neck irradiation, or significant cardiac risk factors. Otherwise, the two techniques have similar risk and benefit profiles as well as 10-year outcomes. A 10-year multicenter prospective trial found that the rate of stroke ipsilateral to endarterectomy was 6.9 percent, and after stenting was 5.6 percent, but this difference did not reach statistical significance (hazard ratio 0.99, CI 0.64 to 1.52) in the 2,502 patients enrolled.[18] The primary risk of carotid artery stenting is transient or permanent neurologic deficits secondary to emboli, dissection, or occlusion of the vessel; other complications of carotid artery stenting include transient bradycardia, hypotension, and those related to femoral artery access.

Although advances in imaging capabilities, catheters, and embolic materials will advance endovascular capabilities, the knowledge, judgment, and experience of the angiographer have the greatest impact on the risks of endovascular therapy.

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CHAPTER

54

Preoperative and Postoperative Care of Patients with Neurologic Disorders

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INTRODUCTION

MOVEMENT DISORDERS
  Special Considerations for Deep Brain Stimulation
  Movement-Disorder Emergencies in the Perioperative Period

MULTIPLE SCLEROSIS

DELIRIUM AND DEMENTIA
  Delirium
  Dementia

HEADACHE
  Migraine
  Medication Overuse
  Caffeine Withdrawal
  Intracranial Hypotension

SEIZURES AND EPILEPSY

NEUROMUSCULAR DISORDERS
  Motor Neuron Disease
  Peripheral Nerve Disorders
  Myopathies
  Myasthenia Gravis

PERIOPERATIVE STROKE
  Incidence
  Pathophysiology and Timing
  Risk Factors
  Risk Factor Modification and Postoperative Stroke Care
  Antithrombotics and Anticoagulation in the Perioperative Period
  Timing of Elective Surgery Following a Stroke
  Perioperative Considerations Pertaining to Carotid Disease

INTRODUCTION

Perioperative care of the patient with neurologic disease provides practitioners with a number of unique challenges ranging from timing of surgery, administration of medications, and anesthetic choices, to postoperative care. This chapter focuses on common neurologic disorders and the perioperative considerations that accompany them.

MOVEMENT DISORDERS

Parkinson disease remains a common neurodegenerative disease particularly among persons over age 70 years. Therefore, thousands of parkinsonian patients will undergo various surgical procedures each year, and many will experience unique perioperative and surgical challenges related to their underlying disorder.

A key factor in caring for parkinsonian patients in any setting is establishing their specific medication regimen and the timing of these medications. Patients with Parkinson disease are often taking medications that prolong the QT interval, and in these patients a preoperative electrocardiogram may be warranted. Antiparkinsonian medications are almost exclusively oral, making challenging the “nil by mouth” (NPO) status prior to surgery and the timing and administration of perioperative medications. The patient’s typical dopaminergic medication regimen should be continued on the day of surgery and as close as possible to the time of anesthesia while monoamine oxidase B inhibitors are generally stopped a few weeks before surgery due to medication interactions. Levodopa has a short half-life, on the order of 1 to 3 hours; if the planned duration of surgery is long and general anesthesia is being employed, consideration should be given to placing a nasogastric tube and continuing levodopa intraoperatively. Missed doses may precipitate a parkinsonian crisis resulting in severe rigidity and akinesia, leading to prolonged intubation and recovery time. The possibility of resting or orthostatic hypotension, which is common in Parkinson disease and a side effect of many

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medications used to treat it, should also be considered, and anesthetic agents that commonly cause hypotension should be avoided.

When a patient is unable to take dopaminergic medications orally in the perioperative period, one strategy is to switch patients to a transdermal dopamine agonist, rotigotine, with a half-life of approximately 24 hours. However, this may be challenging for patients taking a complex oral regimen as conversion between various dopaminergic formulations varies widely from patient to patient.

Regional anesthesia has the added benefit of minimizing postoperative nausea and vomiting, which will allow for the timely resumption of oral medications. If general anesthesia is necessary, halothane should be avoided in patients taking levodopa as it sensitizes the heart to catecholamines. Propofol has been associated with worsening dyskinesias but has also been observed to improve tremor; it is often avoided in patients undergoing deep brain stimulation (DBS) surgery. Antiemetics are commonly administered intraoperatively and postoperatively, but dopamine antagonists such as prochlorperazine and metoclopramide can worsen parkinsonism and block the effects of levodopa therapy; therefore, they should be avoided in favor of ondansetron and domperidone.

Extubation of parkinsonian patients may be complicated. Up to one-third of patients have an obstructive ventilatory pattern related to upper airway dysfunction including laryngeal dysmotility and retained secretions. This dysfunction places parkinsonian patients at increased risk of aspiration. It is critical to resume a patient's home medication regimen as soon as possible with particular adherence to the timing of medications even if it deviates from hospital medication administration times. For patients with dysphagia, carbidopa/levodopa comes in an orally disintegrating formulation and an immediate release formulation that can be administered via feeding tube.

Parkinsonian patients are also at a substantially increased risk of developing postoperative confusion and hallucinations, in some cases due to underlying diffuse Lewy body pathology; therefore, these patients must be monitored carefully in the postoperative setting and strategies to prevent delirium should be planned in advance. An elevated risk of urinary tract infections, aspiration pneumonias, and bacterial infections among parkinsonian patients can result in longer hospital stays and increased perioperative morbidity. Improved surgical outcomes occur when medication regimens are optimized by a neurologist; with early mobilization; when postoperative complications are carefully monitored; and when conversations regarding long-term care and prolonged rehabilitation occur early in the hospitalization.

Special Considerations for Deep Brain Stimulation

DBS is now a well-accepted treatment for medication-resistant Parkinson disease. Given the potential risk of intracerebral hemorrhage with insertion of DBS leads, all antiplatelet medications should be discontinued for 7 to 10 days prior to surgery. Typically, antiparkinsonian medications are discontinued the night before surgery. General anesthesia is avoided so that the patient is awake and parkinsonian symptoms can be monitored intraoperatively. Postoperatively, patients should be kept normotensive to minimize the risk of hemorrhage, and antiparkinsonian medications should be resumed immediately.

Movement-Disorder Emergencies in the Perioperative Period

Perioperative movement-disorder emergencies commonly occur because a patient's usual medication regimen is discontinued or because of new medications introduced in the perioperative period. Diagnosis requires a detailed knowledge of the patient's pre-existing conditions and a careful review of preoperative, intraoperative, and postoperative medications. Patients with Parkinson disease who have their levodopa discontinued suddenly may experience life-threatening parkinsonism-hyperpyrexia, characterized by fever, severe rigidity, autonomic instability, and an elevated serum creatine kinase level. Treatment includes restoration of dopaminergic therapy, and the management strategies discussed later.

Somewhat clinically similar to the parkinsonism-hyperpyrexia syndrome, neuroleptic malignant syndrome results from dopamine receptor blockade. Commonly implicated medications include neuroleptics, antiemetics (e.g., metoclopramide and prochlorperazine), and droperidol, which should be withdrawn promptly. In these syndromes, symptoms may last for days and be life-threatening. Treatment often requires care in the intensive care unit, with aggressive hydration and cooling. Dantrolene, bromocriptine, or amantadine is typically initiated, but the evidence for their efficacy is derived mainly from case reports.

A third and clinically distinct disorder, serotonin syndrome, results from excessive serotonin activity. It may occur as a consequence of drug interactions, overdose of certain medications, or therapeutic (or recreational) drug use. Though rare, of particular note is that patients with Parkinson disease taking monoamine oxidase B inhibitors (e.g., selegiline and rasagiline) are at risk for serotonin syndrome when combined with other serotonergic medications including some antibiotics and opiates (tramadol). Manifestations may include hypertension, tachycardia, hyperthermia, diaphoresis, myoclonus, tremulousness, hyperreflexia, confusion, agitation, and even coma. Treatment involves discontinuation of offending agents and often requires care in the ICU, control of the blood pressure, and management with cyproheptadine or benzodiazepines. A final related condition, discussed later, is malignant hyperthermia, a rare genetic disorder triggered by inhalational anesthetics or succinylcholine.

MULTIPLE SCLEROSIS

Anesthetic and surgical complications related to multiple sclerosis (MS) are relatively rare, but certain preoperative, intraoperative, and postoperative considerations are important. There is not abundant evidence to suggest that anesthesia or surgery consistently leads to disease exacerbations, but physiologic stress is commonly considered a cause of exacerbations and is heightened in the perioperative period. Accordingly, patients should be counseled about the potential risk of MS exacerbation with surgery and monitored for such postoperatively.

Disease-modifying therapies aimed at reducing the frequency and severity of MS exacerbations should be continued in the perioperative period. In patients with low medullary and high cervical demyelinating lesions, ventilatory dysfunction should be anticipated, as respiratory effort may be impaired.

Consideration should also be given to choice of anesthetic and anesthetic technique in patients with MS. Systemic administration of certain local anesthetics (e.g., lidocaine) may unmask clinically silent MS plaques or transiently worsen pre-existing symptoms. Results of studies involving spinal anesthesia are mixed with some demonstrating a higher relapse rate in MS compared to general anesthesia, while others do not. Epidural anesthesia may have a lesser risk than intradural anesthesia due to decreased concentrations of anesthetics penetrating the thecal sac. Overall, the evidence for neuraxial anesthesia affecting neurologic function in patients with pre-existing CNS disorders is not definitive and an individual risk–benefit analysis should be employed when selecting a method of anesthesia.

Although general anesthesia has been linked to MS exacerbations, it has often been used successfully, and there is no solid evidence to suggest that any single intravenous or inhalational anesthetic is preferable to another. If a patient experiences an MS relapse in the immediate postoperative period, the intraoperative temperature recordings should be checked as hyperthermia may cause MS pseudoexacerbations (Uhthoff phenomenon, i.e., symptoms that are not caused by new MS lesions and improve with a return to normothermia).

Caution should also be exercised in patients with MS receiving intrathecal baclofen for spasticity, as abrupt withdrawal may precipitate a potentially life-threatening syndrome characterized by seizures, hallucinations, and autonomic instability. Management includes resumption of baclofen as soon as possible and treatment with high-dose benzodiazepines in the interim.

Patients with MS should be monitored closely in the postoperative period. The appearance of new demyelinating plaques or increased neurologic deficits related to existing plaques may result from the stress of surgery or infection. Such exacerbations may result in impaired respiratory function and in autonomic dysfunction causing labile blood pressure. Baseline neurologic dysfunction in patients with MS combined with the stress of surgery may result in longer recovery times and necessitate rehabilitation upon discharge, even in the absence of any clinical deterioration.

DELIRIUM AND DEMENTIA

Delirium

Delirium is a complex entity characterized by the relatively acute onset of disorientation and attentional deficits that follow a fluctuating course. The incidence of postoperative delirium in the elderly ranges from 10 to 60 percent and varies somewhat with the type of surgery performed (Table 54-1).[1] Due to its variable forms—hyperactive, hypoactive, and mixed—delirium is often under-recognized. Hyperactive delirium involves agitation, combativeness, and hypervigilance, as is commonly seen in alcohol withdrawal. This form is easily recognized by clinicians. The hypoactive form, which may present with lethargy, stupor, or even coma, is sometimes difficult to recognize, as patients are less obtrusive and do not seek care or attention. It is not uncommon

TABLE 54-1 ■ Incidence of Postoperative Delirium in the Elderly by Surgical Type

Type of Surgery	Incidence Range (%)
Cataract	1–3
General	10–14
Orthopedic (mainly hip)	32–55
Open heart	32–79

for these patients to be misdiagnosed with severe depression or for their cognitive dysfunction to be unrecognized.

Research has focused mainly on identifying baseline characteristics that predispose to the development of postoperative delirium and on iatrogenic risks of developing delirium, with relatively less emphasis until recently on the management and the long-term consequences of postoperative delirium. The vast majority of cases of postoperative delirium occur within 3 days of surgery and later onset delirium should raise concern for withdrawal from medications or alcohol.[1] The consensus opinion is that the route of anesthesia, general versus regional, does not have a major impact on the rates of postoperative delirium. However, the type of anesthesia may be relevant when considering the timing of postoperative altered mental status. Patients receiving regional anesthesia tend to maintain or recover cognitive function more quickly than those receiving general anesthesia. Especially in the first 24 to 48 hours, it is important to consider which type of anesthesia the patient received as this may account for differences in mentation.[1]

Factors that are associated with the development of delirium are well established (Table 54-2). It is important to recognize the possibility of postoperative delirium in elderly patients and those with baseline cognitive impairment ranging from mild cognitive impairment to frank dementia. In patients undergoing elective surgery, it is especially important to obtain an accurate history of substance use as both intoxication and withdrawal may manifest as delirium following surgery. Even mild pre- to postoperative electrolyte shifts, such as subtle hypo- or hypernatremia, may result in postoperative delirium. Postoperative pain management poses a particular challenge. Both untreated pain and analgesic use may worsen delirium. There remains a tendency to utilize physical restraints postoperatively to prevent patients from disrupting their wounds; such restraints may increase the risk of delirium and therefore should be discontinued as soon as possible.

TABLE 54-2 ■ Factors Commonly Associated With Delirium

Risk Factors

- Advanced age
- Baseline cognitive impairment
- Infection
    - Urinary tract infection
    - Pneumonia
- Toxic derangements
    - Intoxication
    - Withdrawal (alcohol, benzodiazepines)
- Poor baseline nutritional status (low serum albumin)
- Metabolic derangements
    - Hepatic encephalopathy
    - Uremic encephalopathy
    - Dehydration
    - Hypoxia and hypercarbia
    - Electrolytes: hyponatremia/hypernatremia, hypercalcemia, hypermagnesemia, hypophosphatemia
- Iatrogenic
    - Poor sleep hygiene
    - Physical restraints
    - Urinary catheters
    - Multiple surgical procedures
    - Untreated pain
- Medications
    - Anticholinergics
    - Benzodiazepines
    - Barbiturates
    - Opiates
    - Corticosteroids
    - Muscle relaxants
    - Antibiotics (cephalosporins and fluoroquinolones)

Postoperative delirium has been associated with a number of poor outcomes. Length of stay, postoperative complications, and mortality are known to increase in the setting of postoperative delirium.[2] Such patients are more likely to be discharged to a rehabilitation or long-term nursing facility than those without delirium. It is important to remember that while delirium may only last a few days in many patients, a substantial number of patients will experience delirium that persists until hospital discharge or beyond.[2] Postoperative delirium has also been associated with an increased risk of developing dementia in elderly patients with no known baseline cognitive dysfunction, suggesting that delirium may in itself cause long-term neurologic damage.

Prevention of postoperative delirium is critical, but if postoperative altered mental status develops, the focus should shift to early identification and exclusion of other potentially treatable causes. This workup usually includes neuroimaging to assess for stroke, hemorrhage, or mass lesion; an electroencephalogram (EEG) to evaluate for seizures; and possibly a lumbar puncture to evaluate for evidence of a cerebral inflammatory or infectious disorder. Treatment depends on identification and reversal of the underlying cause. In the postoperative period, delirium precautions should be instituted, including frequent reorientation, opening blinds to allow for natural light to enter, and maintaining normal sleep–wake cycles. Physical restraints should be discontinued as soon as is safe and replaced with close monitoring from nursing staff, sitters, or family members to ensure patient safety. Unnecessary lines and tubes, particularly urinary catheters, should be discontinued. Early postoperative mobilization, even range-of-motion exercises for bedbound patients, and simple acts such as making patients' eyeglasses and hearing aids available are important in treating as well as preventing delirium. Psychoactive medications, particularly anticholinergics, should be discontinued whenever possible. Postoperative pain control should be with minimum levels of analgesics required for relief. If these nonpharmacologic interventions are insufficient, pharmacologic treatment should be considered only if patients pose a risk of direct harm to themselves or the staff, while taking care to avoid the benzodiazepine class of medications, which has a particularly poor cognitive side-effect profile. Common practice is to consider using a low dose of an antipsychotic medication, such as quetiapine, at bedtime.

Dementia

Patients with dementia who undergo surgery require special consideration. It is crucial to establish the patient's preoperative baseline cognitive and physical function with family and caregivers in order to assess accurately their postoperative level of functioning. Patients with dementia are often elderly and have numerous medical comorbidities as well as poor nutritional status, dehydration, and baseline electrolyte abnormalities. These conditions should be optimized or corrected preoperatively in order to maximize recovery and shorten length of hospital stay. Acetylcholinesterase inhibitors used to treat dementia should be continued throughout the perioperative period, although this class of medications may prolong the effects of succinylcholine.

Patients with dementia are at an increased risk of numerous postoperative complications including renal failure, pneumonia, urinary tract infections, sepsis, and strokes. They also have an increased risk of postoperative delirium related to their baseline cognitive impairment and comorbidities.

Postoperative care for patients with dementia mostly revolves around the prevention and treatment of delirium. Pre- and postoperative consultation with geriatrics or neurology can be helpful, and when possible, patients with dementia should be cared for on hospital units that focus on acute care of elderly patients. Although surgery alone may be sufficient to precipitate delirium in a patient with dementia, other triggers should still be investigated. Patients with Alzheimer disease, and probably many other neurodegenerative conditions, are at increased risk of seizures, emphasizing the need to obtain an electroencephalogram for those with an unexplained altered mental state postoperatively. Postoperative pain control can be challenging as patients with severe dementia may not be able to verbalize whether they are in pain. Pharmacologic management of delirium in patients with dementia should be used as infrequently as possible. Benzodiazepines in particular should be avoided, and low-dose antipsychotics should be used sparingly—a US Food and Drug Administration black box warning links antipsychotics to increased mortality among elderly patients. In patients with Lewy body dementia, antipsychotics should be avoided due to their profound sedating and extrapyramidal effects, which may be irreversible. Patients with dementia and their families should be counseled early regarding the possibility of a prolonged postoperative hospital course and the potential for discharge to a rehabilitation or nursing facility; in the setting of elective surgeries, these considerations may impact the decision to proceed.

HEADACHE

A detailed headache history is important when evaluating patients with postoperative headaches, as preexisting primary headache disorders, such as migraine and tension headache, are common and often exacerbated by the stress of surgery and the dehydration that accompanies the NPO status. There are numerous warning features in the history and physical examination that signal the possibility of a secondary headache phenomenon related to a structural brain injury (Table 54-3).

Migraine

Patients with migraine should have their prophylactic medications continued in the perioperative period. Their migraine-abortive agents should also be continued postoperatively, though caution should be exercised when prescribing triptan medications after vascular surgeries given their vasoactive properties. Intravenous hydration with normal saline and administration of antiemetics such as prochlorperazine may be useful for

TABLE 54-3 ■ Common Warning Features Associated With Secondary Headaches

Subjective	Physical Examination
New headache after age 50	Focal neurologic deficit
Change in character of prior headache	Fever
Worsens with Valsalva, exertion, cough, or sneezing	Hypertension
Awakens patient from sleep or typically occurs in the morning	Altered mental status
Associated seizure	Papilledema
Positional component	Meningismus
Thunderclap in onset	Scalp tenderness (especially over temporal artery)
Immunocompromised state	
Jaw claudication	

attacks even when the migraine is not accompanied by significant nausea and vomiting. A brief course of a nonsteroidal anti-inflammatory drug (e.g., naproxen or intravenous ketorolac) may be used in refractory cases. Migraine, particularly that with aura, has been associated with an increased risk of perioperative ischemic stroke and 30-day hospital readmission, although the precise mechanism for this association remains unclear.[3]

Medication Overuse

Analgesic overuse for the treatment of pain including headache is common among the general population as is medication-overuse headache. While postoperative pain may require narcotics, treatment of headaches with short-acting narcotics sometimes exacerbates the primary headache disorder and prolongs the period of recovery. Nearly all agents given to abort headache may be associated with medication-overuse headache. Treatment for this condition is gradual discontinuation of the medication; however, symptoms of opiate withdrawal including headache, nausea, vomiting, tachycardia, and insomnia are common, and therefore these medications are best weaned outside the perioperative period.

Caffeine Withdrawal

Due to the high frequency of consumption, caffeine withdrawal has become a widely recognized source of headache. Cessation of caffeine intake in people with low-to-moderate daily caffeine consumption can result in higher depression scores, fatigue, and headache. Headaches from caffeine withdrawal may begin 24 hours after cessation and last up to 5 or 6 days. In patients with postoperative headache, a careful caffeine history should be taken and—when caffeine withdrawal is responsible—resumption of normal caffeine intake permitted.

Intracranial Hypotension

Dural puncture with resultant intracranial hypotension remains a common cause of perioperative headache after spinal anesthesia and particularly after accidental dural puncture with a large-bore needle during epidural anesthesia. Among such headaches, the vast majority will begin within 48 to 72 hours of the dural puncture. A headache immediately following the procedure should raise suspicion of an alternate etiology. The headache of intracranial hypotension is typically located in the frontal and occipital regions, is exacerbated by an upright posture, and is alleviated by recumbency. Accompanying symptoms may include nausea, vomiting, tinnitus, vertigo, paresthesias, diplopia, and cranial nerve palsies. The findings on magnetic resonance imaging (MRI) of intracranial hypotension include diffuse pachymeningeal enhancement, subdural fluid collections, engorged cerebral venous sinuses, and descent of the cerebellar tonsils (Fig. 54-1).[4]

Prevention of postdural puncture headache involves using a smaller gauge or noncutting needle. Vigorous hydration, caffeine, gabapentin, theophylline, and hydrocortisone have some efficacy in the treatment of such headaches. Epidural blood patch remains the mainstay of treatment; providing complete or partial relief in a large majority of patients. If the initial blood patch does not relieve symptoms, a second blood patch should be administered, often with an extended period of lying supine following the procedure.

SEIZURES AND EPILEPSY

Epilepsy is a common neurologic disorder and perioperative seizures are seen in approximately 2 to 6 percent of persons with epilepsy.[5] The most important predictors of perioperative seizure risk are baseline seizure frequency and timing of most recent seizure, particularly in the month preceding surgery. Patients with epilepsy should be advised to take their antiepileptic medications on the morning of surgery, and these medications should be resumed as soon as possible postoperatively. Preferably, these drugs should be administered orally,

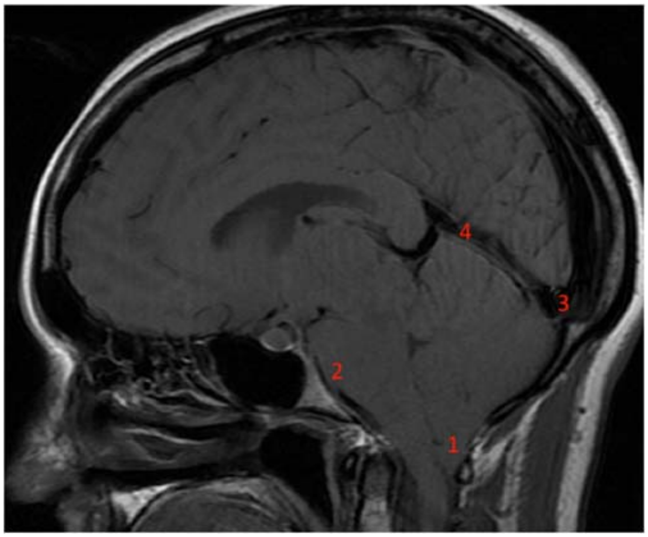

FIGURE 54-1 ■ Noncontrast sagittal T1 magnetic resonance image of a patient with cerebrospinal fluid leak and resultant intracranial hypotension. Image demonstrates downward descent of the cerebellar tonsils (1), effacement of the prepontine cistern with the pons apposed to the clivus (2), and prominent venous vasculature including the torcula (3) and straight sinus (4).

although intravenous preparations of phenytoin, sodium valproate, levetiracetam, phenobarbital, lacosamide, and benzodiazepines are an alternative for those with limited oral intake. Oral and intravenous dosages are largely equivalent, but the frequency of administration may vary from one preparation to another, and some extended-release formulations may not be easily converted to an intravenous dose.

Both phenytoin and fosphenytoin can precipitate hypotension and arrhythmias with rapid intravenous infusion; however, fosphenytoin can generally be infused at a faster rate and with a lower risk of local adverse effects following extravasation, and therefore is the intravenous phenytoin preparation of choice. Phenytoin can be administered via feeding tube, but levels are altered by enteral feedings, making the intravenous preparation preferable in such instances.

Antiepileptic drug levels need not be checked routinely in the perioperative period unless there has been a recent change in seizure frequency or concern for drug toxicity. Antiepileptic medications have many drug interactions, particularly in the case of the cytochrome P-450–inducing agents phenytoin, carbamazepine, phenobarbital, and primidone, which can result in decreased levels of many medications including some antibiotics, immunosuppressants, analgesics, and neuromuscular blocking agents.

It is widely believed that some general anesthetics can have both pro- and anticonvulsant properties depending on the dose and clinical situation. Enflurane, sevoflurane, and etomidate induce epileptiform activity on the EEG and should generally be avoided in patients with epilepsy, while isoflurane and halothane have anticonvulsant properties.[5] Intravenous anesthetics including barbiturates and propofol are used for the treatment of status epilepticus, but at induction have been reported to be excitatory and can rarely precipitate a seizure. Some opioids, particularly meperidine and to a lesser extent fentanyl, have been linked to seizures, especially with intrathecal use. Propofol and opioids can also cause myoclonus and tremulousness that may clinically mimic seizures. Neuromuscular blocking agents have not been linked to seizures; however, if seizures are suspected while these drugs are being administered, continuous electroencephalographic monitoring is required as clinical manifestations of seizures will be masked.

Evidence regarding the epileptic potential of local anesthetics is conflicting. While they can cross the blood–brain barrier, evidence that they increase the risk of perioperative seizures is lacking.

Postoperative seizures should be considered as an etiology for delayed awakening after anesthesia. A relatively high frequency of seizures has been found in patients with altered mental status or “spells,” both in the intensive care unit and in general medical wards. If possible, an extended electroencephalogram should be obtained to exclude nonconvulsive seizures, but this should not delay treatment in cases where the suspicion of seizures is high.

The evaluation of perioperative seizures is similar to the evaluation of seizures occurring in other settings. Consideration should be given to withdrawal syndromes, missed doses of antiepileptic medications or malabsorption of medications, medication interactions, metabolic derangements (e.g., hyponatremia, hypocalcemia, hypomagnesemia, glucose shifts), infection, and structural brain abnormalities. Treatment should focus on stopping seizures promptly and correcting obvious provoking factors.

NEUROMUSCULAR DISORDERS

Neuromuscular diseases present the neurologist, surgeon, and anesthesiologist with some important general considerations common to this group of disorders as well as challenges inherent to specific diseases. All patients with severe neuromuscular disease are at risk of increased ventilatory complications due to respiratory weakness, and preoperative pulmonary assessment with forced vital capacity (FVC) and maximal inspiratory force should be performed. Complications in patients with respiratory weakness include an increased sensitivity to respiratory depression from opioids, barbiturates, and benzodiazepines, as well as difficulty in weaning from the ventilator. Patients with some neuromuscular disorders including the muscular dystrophies have an increased risk of life-threatening cardiac dysrhythmias along with depressed cardiac contractility, warranting a preoperative assessment with electrocardiography and echocardiography. Depolarizing neuromuscular blockers such as succinylcholine can lead to hyperkalemia and resultant cardiac dysfunction in these patients and should be avoided.

Motor Neuron Disease

The timing of surgical procedures and anesthetic choice in patients with amyotrophic lateral sclerosis is important given an often profound progressive underlying respiratory weakness. Measurement of preoperative FVC is critical as an FVC of less than 50 percent predicted is associated with higher likelihood of postoperative respiratory failure. Noninvasive positive-pressure ventilation can be used to prevent pulmonary complications in the immediate postoperative period and reduce the chances of reintubation. Nondepolarizing neuromuscular blockade may precipitate severe weakness in patients with amyotrophic lateral sclerosis. However, due to the previously described effects of succinylcholine in many neuromuscular disorders, low doses of nondepolarizing blockers are preferred when neuromuscular blockade is necessary. Regional and epidural anesthesia may be used safely in these patients without exacerbating neurologic symptoms. Given the potential complications and prolonged recovery times following anesthesia and surgery, a multidisciplinary preoperative approach with cardiac and pulmonary screening is warranted, with appropriate preoperative counseling of the patient and family members regarding these risks.

Peripheral Nerve Disorders

Diabetic autonomic neuropathy is a relatively common complication of both type 1 and type 2 diabetes. Poor glycemic control and duration of disease are felt to be risk factors for the development and progression of the neuropathy. These patients are at increased risk of significant bradycardia during induction of anesthesia as well as intraoperative hypotension requiring vasopressor support. Although there are no specific guidelines for anesthetic choice, etomidate and opioids may minimize hemodynamic instability while thiopental and propofol may carry a higher risk of hypotension.

Charcot–Marie–Tooth disease, the most common hereditary motor and sensory polyneuropathy, is associated with autonomic dysfunction as well as respiratory muscle weakness in a minority of patients. While few complications have been reported for patients with Charcot–Marie–Tooth disease undergoing surgery, succinylcholine provides a theoretical risk for complications and should be avoided if at all possible.

Case series describe surgery as a potential trigger for acute inflammatory demyelinating polyradiculoneuropathy (AIDP; Guillain–Barré syndrome), a relatively common cause of acute paralysis. The precise mechanism for this association is unknown, but one theory is that surgery alters the immune system, igniting a pathway leading to molecular mimicry against peripheral nerve components, perhaps in the setting of postoperative infection.

With both AIDP and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), perioperative FVC and maximal inspiratory force should be monitored serially to provide some indication as to whether a patient can be extubated safely. Patients with AIDP and CIDP are sensitive to nondepolarizing muscle relaxants, which may necessitate prolonged postoperative ventilation when administered. Reports of worsening neurologic function in patients with AIDP following epidural anesthesia exist. Local anesthesia has been linked to hypotension, bradycardia, and cardiac complications in patients with AIDP, presumably due to involvement of the autonomic nervous system. There are no firm recommendations regarding the preferred anesthetic technique for patients with AIDP and CIDP.

Myopathies

Patients with muscular dystrophies including Duchenne, Becker, and Emery–Dreifuss often undergo a series of surgeries in their lifetime involving tendon releases and correction of scoliosis. Due to the systemic nature of these disorders, a multidisciplinary perioperative approach involving a neurologist, pulmonologist, cardiologist, and anesthesiologist is often warranted. Many of these disorders are associated with cardiomyopathy and disorders of cardiac conduction. Respiratory function is often compromised because of ventilatory muscle weakness as well as poor mechanics secondary to skeletal abnormalities. A thorough preoperative pulmonary evaluation including measurement of FVC, maximal inspiratory force, and peak cough flow should be strongly considered. Patients found to have a FVC of less than 50 percent of the predicted value should be considered for preoperative training of noninvasive positive-pressure ventilation, given the risk of ventilatory compromise following surgery. Most muscular dystrophies are not linked to an increased incidence of malignant hyperthermia. Inhaled anesthetics such as halothane have been associated with rhabdomyolysis in the absence of succinylcholine in patients with elevated serum creatine kinase levels at baseline.

Patients with other myopathies face similar risks associated with surgery and anesthesia. Reports of hyperkalemic cardiac arrest in children undergoing anesthesia have been linked to previously unrecognized myopathies. Central core myopathy, an autosomal dominant disorder, has been closely linked to malignant hyperthermia, via a common mutation in the ryanodine receptor gene (*RYR1*). The prevalence of malignant hyperthermia has been estimated at 1 per 100,000 hospital discharges in all patients. This rare genetic condition is triggered by exposure to inhalational anesthetics or succinylcholine in susceptible individuals and is characterized by muscle rigidity, tachycardia, hyperthermia, hypercapnea, and metabolic acidosis. Malignant hyperthermia or a malignant hyperthermia-like syndrome has been described in a variety of myopathies and channelopathies (e.g., periodic paralysis). The mainstay of treatment for malignant hyperthermia other than supportive care remains dantrolene, which decreases skeletal muscle calcium release, thereby inhibiting muscle contraction. If anesthesia is required in patients with myotonic dystrophy, depolarizing muscle-relaxant drugs should be avoided because they may cause myotonic spasm, and nondepolarizing drugs are given in reduced dosage to patients who are taking quinine for their myotonia.

Myasthenia Gravis

Myasthenia gravis (MG) is the most common neuromuscular junction disorder, and consequently most of the research into the perioperative care of patients with such disorders has focused on MG. The preoperative care of patients with MG begins with appropriate counseling of the patient and family, emphasizing that the stress associated with elective surgery may temporarily worsen the disease, necessitate postoperative care in the intensive care unit, and lead to prolonged intubation. Since thymectomy is a treatment for MG, this surgery provides a natural avenue to study the perioperative care of patients with MG. A study of risk stratification of patients with MG undergoing thymectomy demonstrated that disease duration of greater than 6 years, coexistent chronic respiratory disease, daily pyridostigmine dose exceeding 750 mg, and a FVC of less than 2.9 liters predicted the need for postoperative ventilation.[6] This predictive tool may not apply to patients with MG undergoing surgeries other than thymectomy. A preoperative neurologic examination focusing on facial strength, dysarthria, dysphagia, neck flexion strength, and formal pulmonary function testing, especially in those patients with bulbar weakness, allows for anticipation of postoperative ventilatory compromise and pulmonary complications including aspiration.

Studies have investigated the effects of pyridostigmine on neuromuscular blockade in the perioperative period. There is not sufficient evidence to conclude that changing a patient's pyridostigmine dose prior to surgery significantly impacts neuromuscular blockade or the duration of ventilation, and thus the general recommendation is to continue the patient's usual preoperative regimen. Most immunosuppressants in patients with MG do not interact with anesthetics; however, azathioprine extends the effect of succinylcholine and inhibits nondepolarizing neuromuscular blockers.

Elective surgeries should be undertaken when respiratory function is stable and patients are on the lowest possible doses of corticosteroids. In the case of more urgent surgery, presurgical plasma exchange or treatment with intravenous immunoglobulin should be considered to optimize preoperative respiratory status. These preoperative treatments have the potential to decrease the duration of postoperative ventilation and length of stay in the intensive care unit.

When possible, regional anesthesia is preferable to general anesthesia in patients with MG, as it minimizes the need for neuromuscular blockade and ventilation. Patients with MG have a decreased number of functional acetylcholine (ACh) receptors and thus their response to neuromuscular blockade may be abnormal during general anesthesia. Patients may have a prolonged blockade when either succinylcholine or nondepolarizing neuromuscular blockers are used. The dosing of neuromuscular blockade should be individualized based on the severity of the patient's myasthenia; however, 50 percent of a routine dose is likely adequate and an extended recovery time should still be anticipated.

Postoperative recovery in patients with MG may be prolonged. Electrolytes, particularly potassium, should be monitored closely, as hypokalemia may worsen weakness in MG. Whenever possible, postoperative analgesia should be minimized and opioids, benzodiazepines, and barbiturates should be avoided if possible due to their respiratory depressant effects. Patients with MG should have their medications reviewed frequently to ensure that they are not receiving drugs that may worsen weakness, such as aminoglycosides. If pyridostigmine cannot be given orally, the parenteral dose should be administered at roughly one-thirtieth of the enteral dose. Atropine should be given before or concurrent with intravenous pyridostigmine to prevent bradycardia and excessive bronchial secretions. Although no precise clinical criteria can determine the timing of extubation, clinical examination including evaluation of neck flexor strength can guide the decision. After extubation, aggressive pulmonary toilet and use of incentive spirometry should be encouraged. Early mobilization shortens the duration of recovery.

Postoperative myasthenic crisis is not uncommon in patients with MG, occurring in up to one-third of patients. The likelihood of postoperative crisis has been related to a prior history of myasthenic crisis, preoperative bulbar weakness, preoperative serum ACh receptor antibody levels, and intraoperative blood loss. Management should involve urgent assessment of the patient's respiratory status, recognizing that intubation is usually necessary. Effective treatment options include prompt initiation of plasma exchange or intravenous immunoglobulin.

PERIOPERATIVE STROKE

Incidence

The incidence of perioperative stroke, defined as stroke within 30 days following surgery, varies with the type of surgery being performed (Table 54-4).[7–12] The incidence is relatively low among general surgeries but increases in those patients with a history of stroke or transient ischemic attack (TIA). Cardiac and aortic surgeries are associated with the highest risk of perioperative stroke, and this incidence increases with a number of intraoperative factors. Aortic manipulation in the setting of known ascending aortic atherosclerosis increases stroke risk. Similarly, cerebral hypoperfusion related to intraoperative hypotension or reduced cardiac output, as can be seen with use of cardiopulmonary bypass, confers an increased stroke risk. Additional discussion regarding stroke after cardiac surgery in children can be found in Chapters 3 and 4. The risk of perioperative stroke following carotid endarterectomy for symptomatic carotid stenosis has not changed significantly over time from the combined risk found in the European Carotid Surgery Trial and the North American Symptomatic Carotid Endarterectomy Trial. The type of anesthesia, general versus regional, has not been shown definitively to affect the perioperative stroke risk in patients undergoing carotid endarterectomy and should be a joint decision involving the patient, surgeon, and anesthesiologist. Regional anesthesia has the advantage of allowing for intraoperative monitoring of neurologic function in an awake patient.

TABLE 54-4 ■ Incidence of Perioperative Stroke

Type of Surgery	Incidence (%)
General (no prior history of stroke)[7,8]	0.1–0.8
General (prior history of stroke)[9]	2.9
CABG[10]	3.8
Head and neck[11]	4.8
Cardiac valve[10]	4.8–8.8
CABG plus cardiac valve[10]	7.4
Aortic[12]	8.7
Multiple cardiac valves[10]	9.7

CABG, coronary artery bypass graft.

Pathophysiology and Timing

The majority of perioperative strokes are ischemic, and a significant proportion demonstrate multiple areas of infarction, suggesting an embolic etiology. A minority of perioperative strokes are recognized immediately after the procedure itself, with the majority detected within the first 1 to 2 days postoperatively. Early embolic strokes in the postoperative period have been attributed to physical manipulation of the heart or aorta during surgery leading to unstable plaque that can break off in the coming days, while more delayed embolic strokes may result from atrial fibrillation or decreased cardiac output in the postoperative period. Notably, intraoperative hypoperfusion does not appear to be a common etiology for perioperative stroke but should be considered in the setting of deep watershed infarcts ipsilateral to carotid stenosis.[11]

Risk Factors

Both preoperative and postoperative risk factors can be identified and largely follow general cardiovascular disease risk factors. Perhaps the most important preoperative risk factor is the presence of a prior stroke or TIA and risks related to timing of surgery following a stroke are discussed below. A history of hypertension, diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, decreased cardiac output, atrial fibrillation, aortic atherosclerosis, and female sex also serve as preoperative stroke risk factors. Additional preoperative risk factors include recent myocardial infarction, pre-existing renal failure, and increased age. Carotid stenosis and discontinuation of antithrombotic therapies are discussed separately.

Postoperative risk factors for stroke include the combination of low cardiac output and atrial fibrillation. Blood loss (intraoperative or postoperative), hypotension, and dehydration may contribute to a hypercoagulable state leading to an increased risk of postoperative stroke.

Risk Factor Modification and Postoperative Stroke Care

In patients with recent stroke or TIA, it is important preoperatively to determine the etiology and whether it was treated appropriately. In cases of possible or known aortic atherosclerosis, the extent of the atherosclerotic plaque can be assessed preoperatively with transesophageal echocardiography, since some surgical techniques may need to be modified in order to minimize the risk of plaque rupture. Some patients with otherwise unexplained stroke will be found to have atrial fibrillation with extended cardiac telemetry.

New-onset atrial fibrillation following cardiac surgery occurs in 30 to 50 percent of patients.[11] The peak incidence occurs on postoperative days 2 to 4, and consideration should be given for postoperative cardiac telemetry monitoring. Evidence regarding initiating β-blockers in the preoperative period is mixed in relation to stroke risk; however, patients with known atrial fibrillation should have their antiarrhythmic and rate-controlling medications continued throughout the perioperative period and those that were anticoagulated preoperatively should have their anticoagulation resumed as soon as possible in the postoperative period.

The duration of surgery, particularly the amount of time spent on cardiopulmonary bypass, should be minimized to decrease the perioperative stroke risk. Care should be taken to avoid manipulation of plaque in patients with aortic atheromas. There is a lack of robust data to suggest an optimal intraoperative blood pressure range. In general, care should be taken to maintain a patient's blood pressure near their baseline range, particularly if a patient is known to have intracranial stenoses.

Stroke care in the postoperative period differs in some respects from stroke care in other circumstances. Preoperative statin use, regardless of cholesterol levels, decreases a variety of postoperative cardiac and cerebrovascular events (e.g., death from cardiac causes, myocardial infarction, unstable angina, and stroke) in patients undergoing vascular surgery and poses little risk. Intravenous tissue plasminogen activator is contraindicated following major surgery but many reports document the safety of intra-arterial thrombolysis or thrombectomy for perioperative stroke.

Antithrombotics and Anticoagulation in the Perioperative Period

A recent prospective, randomized, double-blind placebo-controlled trial examined perioperative aspirin use for patients with cardiovascular disease undergoing noncardiac surgery.[13] The use of perioperative aspirin was not associated with a decrease in death or nonfatal MI but was associated with an increased risk of major bleeding. Starting aspirin in patients who had not been taking it preoperatively was associated with a decreased risk of stroke but the absolute number of events was very small. The decision to start or stop aspirin perioperatively is individualized and should involve a multidisciplinary discussion. Based on this trial, a general recommendation is to not initiate aspirin preoperatively in patients who are not already taking it and to hold aspirin for 5 to 7 days prior to major surgery in patients who are taking aspirin and are undergoing noncardiac surgery. Postoperatively, aspirin should be resumed as soon as is safe from a surgical perspective in patients with a long-term indication for the medication. Importantly, this recommendation should not apply to patients with prior cardiac or carotid stents, particularly those taking dual antiplatelet therapy, and the trial did not include patients undergoing carotid endarterectomy or intracranial surgeries.

Less data are available for other antiplatelet agents such as clopidogrel, but similar recommendations likely apply. When being used for stroke prevention, clopidogrel should be discontinued approximately 3 to 7 days prior to noncardiovascular surgery. Antiplatelet medications should generally be continued through the perioperative period for patients undergoing carotid endearterectomy.

The decision to continue or interrupt anticoagulation during the perioperative period is complex. In the absence of rigorous data, one must balance the risk of thromboembolic events against the risk of major hemorrhage. Neurologists commonly encounter this clinical dilemma in patients who are anticoagulated for atrial fibrillation. Examples of patients at high risk for thromboembolic events include those with atrial fibrillation who have experienced a recent stroke or those patients with a prosthetic heart valve. For procedures with a low risk of bleeding including dental procedures, endoscopy, colonoscopy, and cataract surgery among others, it is often best to continue anticoagulation without interruption, particularly in patients at high risk for thromboembolism.

When interrupting anticoagulation, it is important to consider whether the patient is taking warfarin or a direct oral anticoagulant. Warfarin should be stopped approximately 5 days prior to planned surgery and the prothrombin time and international normalized ratio checked prior to surgery. Warfarin can generally be restarted within 12 to 24 hours of an uncomplicated surgery as it often takes 5 days or more to reach full anticoagulant effect. Direct oral anticoagulants should generally be stopped 2 to 3 days prior to surgery, but the half-life of the specific agent involved should be considered. Since these medications rapidly achieve anticoagulant effect, they should only be resumed when safe from a postoperative hemorrhage standpoint.

The decision to bridge with a short-acting anticoagulant such as low-molecular-weight heparin again involves assessing the risk of thromboembolism versus hemorrhage. In selected patients who are at high risk for thromboembolism and in whom surgery cannot be delayed, bridging anticoagulation can be considered. However, in studies of patients receiving warfarin or direct oral anticoagulants for atrial fibrillation, forgoing bridging anticoagulation was not inferior to bridging with low-molecular-weight heparin when examining thromboembolic events, and this strategy reduced the risk of major hemorrhage.[14,15]

Timing of Elective Surgery Following a Stroke

There are few data to guide the timing of elective surgery following a stroke or TIA. Recent stroke or TIA patients require a thorough evaluation of stroke etiology prior to being considered for elective surgery. This should include evaluation of the carotid arteries as carotid endarterectomy may be warranted prior to elective surgery for symptomatic disease. Delaying elective surgery following a stroke or TIA is based on an increased risk of recurrent stroke in the immediate postevent period due to changes in cerebral autoregulation and ongoing inflammation as the brain heals. Accordingly, delaying elective surgery for 3 months or more appears to be sufficient to allow for elimination of this added risk but must be balanced against the risk of delaying an individual surgery. In cases where surgery cannot be delayed, patients should be counseled about the increased risk of recurrent stroke as part of the surgical consent process.

Perioperative Considerations Pertaining to Carotid Disease

Discovery of a carotid bruit is not uncommon as part of the preoperative clinical evaluation. An asymptomatic carotid bruit is a marker of general vascular disease but does not correlate with severity of carotid stenosis. Asymptomatic carotid bruits generally do not require further evaluation unless a surgery is planned with a high risk of hypotension, as unilateral asymptomatic stenosis alone does not increase perioperative stroke risk. If the carotid stenosis is symptomatic (e.g., symptoms of a stroke or TIA over the past 6 months), imaging should be undertaken.

The decision to recommend carotid endarterectomy prior to another surgery remains controversial in many cases and depends on whether the patient's carotid stenosis is symptomatic or asymptomatic, unilateral or bilateral, and the type of surgery planned. Unilateral asymptomatic carotid stenosis generally does not require intervention prior to another surgery, but in cases of asymptomatic, severe bilateral carotid stenosis, preoperative carotid surgery may be considered, particularly if a cardiac surgery is planned that carries a high risk of intraoperative hypotension. In patients with recently symptomatic severe carotid stenosis who require routine or elective cardiac or vascular surgery, the recommendation is to perform carotid endarterectomy within 2 weeks of the cerebrovascular event for nondisabling stroke or TIA and to delay elective surgeries until after the endarterectomy. Patients with concomitant symptomatic carotid and cardiac disease requiring more urgent cardiac surgery are complicated. Studies examining a staged approach where carotid endarterectomy is performed prior to cardiac surgery compared with performing the two procedures simultaneously demonstrated no significant differences in mortality or neurologic complications between the two approaches and found that the staged procedure was associated with a higher overall complication rate.

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CHAPTER

55

Neurologic Disorders and Anesthesia

ALEJANDRO A. RABINSTEIN

PERIOPERATIVE MENTAL STATUS CHANGES
  Postoperative Coma and Delayed Awakening
  Postoperative Delirium
POSTOPERATIVE NEUROLOGIC DEFICITS
  Cognitive Dysfunction
  Paraparesis
  Neuropathy
  Transient Neurologic Symptoms
  Visual Loss
  Hearing Loss
  Cranial Nerve Palsies
PERIOPERATIVE RIGIDITY
PERIOPERATIVE SEIZURES
PERIOPERATIVE HEADACHE
ANESTHESIA IN PATIENTS WITH NEUROLOGIC DISEASE
  Alzheimer Disease
  Parkinson Disease
  Epilepsy
  Other Chronic Diseases of the Central Nervous System
  Neuromuscular Disorders
ANESTHESIA IN THE NEUROCRITICAL CARE UNIT

Current rates of anesthetic complications are low regardless of the type of anesthesia (general, regional, or local). Yet among the complications that may occur, those affecting the nervous system are perhaps the most feared (Table 55-1). This chapter reviews anesthetic-related perioperative neurologic problems as well as perioperative complications that are not caused by anesthesia but are often erroneously attributed to it. Considerations regarding the challenges of anesthesia in patients with established neurologic disease are considered but are discussed in more detail in Chapter 54.

PERIOPERATIVE MENTAL STATUS CHANGES

Postoperative Coma and Delayed Awakening

Failure to arouse and delayed awakening are the most common early neurologic problems following general anesthesia. True prolonged postoperative coma is relatively uncommon, with estimates ranging from 0.005 to 0.08 percent following general surgery, but with higher rates reported after cardiac surgery.[1] Advanced age, urgent surgery, pre-existing brain disorders, perioperative hypotension, postoperative organ failure, and sepsis are independently associated with postoperative coma.[1]

Delayed emergence from anesthesia is the most common cause of early failure to regain alertness after surgery; although this situation is benign, more serious alternative causes include stroke, hypoxic-ischemic brain injury, and status epilepticus. Sepsis and multiorgan failure may produce severe encephalopathy and prolong unresponsiveness, sometimes for days after their resolution. The main causes of impairment of consciousness following surgery are found in Table 55-2.

When a neurologist is asked to evaluate an unresponsive patient following surgery, the principal goal is to determine whether any form of severe acute neurologic disease is responsible. It is therefore important to obtain a detailed history of the patient's preoperative status, review pertinent intraoperative information, and clarify the condition of the patient since surgery. In these situations, direct communication with the anesthesia and surgical teams may provide additional relevant information, such as the presence of clinical features suggesting seizure occurrence or a history of immediate awakening followed by unconsciousness, the latter suggesting cerebral embolism or seizures. It should be determined whether the patient during or immediately after surgery became hypoxemic, hypotensive, or had marked lability of blood

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TABLE 55-1 ■ Major Neurologic Complications of Different Types of Anesthesia

General Anesthesia
Postoperative coma and delayed awakening
Postoperative delirium
Postoperative cognitive dysfunction
Seizures
Malignant hyperthermia
Worsening or relapse of pre-existing neurologic disease
Ischemic optic neuropathy
Regional Anesthesia
CNS toxicity
Postoperative cognitive dysfunction
Seizures
Headache after dural puncture
Epidural hematoma
Epidural abscess
Neuropathy
Transient pain in buttocks and legs
Worsening or relapse of pre-existing neurologic disease
Ischemic optic neuropathy
Transient hypoacusis
Cranial nerve palsies
Local Anesthesia
Neuropathy

From Rabinstein AA, Keegan MT: Neurologic complications of anesthesia: a practical approach. Neurology Clin Pract 3:295, 2013, with permission.

pressure; profuse blood loss; poor hemostasis; or cardiac arrhythmias. Intraoperative hypotension and fluctuations in hemodynamic parameters are common in patients with postoperative coma following cardiovascular surgery.

The general clinical examination is important. A slow respiratory pattern and darkened skin color raise the possibility of CO_2 narcosis. An irregular pulse may signify atrial fibrillation and its increased risk of postoperative stroke. Splinter hemorrhages in the conjunctiva or nail bed suggest fat embolism after long-bone fracture surgery. The neurologic examination should focus on the assessment of level of consciousness, brainstem reflexes, gaze (conjugate versus dysconjugate, presence of skew deviation), eye movements (roving, ocular dipping or bobbing, nystagmoid jerks), muscle tone, response to central (sternal or supraorbital) and peripheral (limb) pain, and presence of adventitious movements. The presence of lateralizing signs requires brain imaging. Brainstem findings or bilateral focal signs should raise suspicion of basilar thromboembolism, prompting vessel imaging. Subtle abnormal movements of the eyes, facial muscles, or fingers may be the only manifestations of underlying status epilepticus and necessitate urgent electroencephalography (EEG). Drug toxicity should be suspected in patients with rigidity, hyperreflexia, and tremors, with or without concurrent fever. Myoclonus may occur with any toxic or metabolic encephalopathy, but can also follow severe global brain anoxia. Asterixis may be a sign of hyperammonemia but also occurs in other metabolic encephalopathies and as a side effect of medications. In patients lacking motor responses following pharmacologic neuromuscular blockade, it must be determined—sometimes by nerve-stimulation studies—whether blockade is continuing; when paralysis is persistent, administration of an antidote may require consideration.

Additional testing is directed by the history and physical findings. If the examination is reassuring and nonfocal, further investigations can be postponed. Brain imaging is indicated in patients with new focal deficits. Computerized tomography (CT) scan is reliable for the detection of acute hemorrhage and can document territorial ischemic infarctions and massive brain edema. Magnetic resonance imaging (MRI) may be necessary to diagnose an embolic shower and subtle manifestations of global hypoxic-ischemic injury such as early cortical injury. In patients with brainstem signs, MRI of the brain can be combined with MR angiography to exclude vertebrobasilar occlusion. EEG should be reserved for those with suspected seizures, and the use of continuous monitoring may increase the diagnostic yield. Lumbar puncture is rarely necessary in patients with postoperative encephalopathy unless central nervous system infection is suspected. Serum studies should be used judiciously, including arterial blood gas to exclude CO_2 retention, as well as determination of glucose, sodium, creatinine and blood urea nitrogen, and ammonia to exclude various metabolic disturbances.

A history of delayed arousal after a previous surgery makes a diagnosis of delayed emergence from anesthesia more likely. Older age and renal and hepatic insufficiency may compromise drug metabolism and clearance, increasing the risk of delayed arousal. Review of the anesthesia course may guide the use of naloxone (for reversal of opioid effect), flumazenil (to reverse benzodiazepines), and physostigmine (to reverse neuromuscular blockade) in appropriate cases.

The prognosis of patients with postoperative coma varies markedly depending on etiology. Although the prognosis is favorable in patients with reversible toxic or

TABLE 55-2 ■ Common Etiologies of Postoperative Impairment of Consciousness

Prolonged Anesthetic and Analgesic Effect
Advanced age
Decreased metabolism and clearance
Toxic Encephalopathy
Perioperative drugs (e.g., benzodiazepines, opiates, serotoninergic agents)
Drug interactions
Metabolic Encephalopathy
Renal failure
Liver failure
Hypercapnia and hypoxia
Hypoglycemia
Hyponatremia and other electrolyte abnormalities
Hyperosmolality
Acidemia
Septic Encephalopathy
Acute stroke
Ischemic
Thromboembolism
Fat embolism
Air embolism
Hemodynamic hypoperfusion
Hemorrhagic
Seizures and status epilepticus (convulsive and nonconvulsive)
Hypoxic/ischemic global brain injury

metabolic causes, the mortality may exceed 80 percent in patients with multifocal infarctions revealed by brain MRI. In survivors of prolonged postoperative coma, long-term functional outcome is frequently poor.

Postoperative Delirium

Postoperative delirium is common, with a reported incidence as high as 40 to 60 percent of patients.[2] Delirium can occur immediately following anesthesia or after some interval from a seemingly normal recovery from the anesthetic; the latter is more commonly persistent and often multifactorial in etiology. The risk of delirium is increased in the elderly and in patients with previous cognitive impairment, a history of substance use (including alcohol), and those receiving polypharmacy before surgery and narcotics or benzodiazepines perioperatively.[2] A previous episode of postoperative delirium predicts recurrence. Perioperative hypoxemia and hemodynamic instability, profuse intraoperative blood loss, and postoperative organ failure may also increase the risk of postoperative delirium. There is limited evidence that the type and route of anesthesia influence the risk of postoperative delirium, with higher rates following general anesthesia.

Evaluation of patients with postoperative delirium begins by considering risk factors for its development (see Table 54-2 in Chapter 54). Time should be spent reviewing the medications that the patient was taking prior to surgery and those administered during and after the operation. Toxic and metabolic factors are the most frequent causes. Exclusion of acute structural brain injury, seizures, and meningoencephalitis (a rare cause of perioperative coma) is the primary responsibility of the consulting neurologist. Primary neurologic diagnoses to be considered include ischemic infarctions (often bilateral or in the brainstem), intracranial hemorrhage (intraparenchymal, subdural, or rarely subarachnoid), nonconvulsive status epilepticus, and posterior reversible encephalopathy syndrome.

Management of delirium depends on its cause. Discontinuation of sedatives and narcotics is often the only intervention required. When agitation is present and patients may harm themselves or others, oral quetiapine, olanzapine, or, in more severe cases, intravenous haloperidol may be necessary, although these medications have not been shown to be effective in usual cases of delirium. Dexmedetodimine, a central α_2-adrenergic agonist, is particularly useful for additional sedation or when agitation is accompanied by sympathetic hyperactivity. Benzodiazepines may worsen delirium and therefore should be reserved for specific indications, such as alcohol withdrawal.

In most cases, postoperative delirium is transient and reversible. Complications sometimes stemming from it include aspiration, self-removal of the endotracheal tube or indwelling catheters, and delays in mobilization that, in turn, result in an increased risk of thromboembolism, infections, and deconditioning. In addition, the occurrence of postoperative delirium is related to a greater risk of postoperative cognitive dysfunction, particularly during the first few months following surgery.[2,3]

POSTOPERATIVE NEUROLOGIC DEFICITS

Cognitive Dysfunction

Postoperative cognitive dysfunction after exposure to general anesthesia occurs more often in older patients and in those with postoperative delirium.[3,4] Mild global cognitive decline is typically observed, although short-term memory and executive function are predominantly affected. Its incidence is greatest after major cardiovascular surgery, ranging from 30 to 80 percent during the first few weeks after surgery and 10 to 60 percent after 3 to 6 months.[3] Patients undergoing noncardiac surgery may also develop postoperative cognitive dysfunction, which has been shown to be associated with the occurrence of perioperative infarctions detectable by MRI.[5] Additional risk factors include alcohol abuse, lower educational level, and previous stroke. Patients affected by this complication, even when transient, may have worse long-term cognitive outcomes, greater disability (particularly in the elderly), and a higher mortality.[3] The impact of anesthesia exposure in early life (i.e., neonates and infants) on subsequent intellectual development has been quite extensively investigated but remains a matter of persistent debate due to inconsistent results across studies.[6]

There is no definitive evidence that the choice of anesthetic regimen (such as general or regional anesthesia) or the depth of anesthesia alters the risk of postoperative cognitive dysfunction. Activation of neuroinflammatory responses has been proposed as a key mechanism underlying the development of cognitive changes after exposure to anesthesia and surgery.[7] Maintenance of physiologic homeostasis during and after surgery may minimize the risk of this complication.

Paraparesis

Epidural hematoma is probably the most feared complication of spinal and epidural anesthesia (Table 55-3). Although rare, patients at higher risk include those with advanced age, alcoholism, anatomic abnormalities of the vertebral column leading to difficulties with needle placement, and, most importantly, coagulopathy due to a bleeding diathesis or anticoagulant effect.[8]

Symptoms of epidural hematoma typically present within the first few hours after the surgery. Attributing them to anesthetic effects may delay the diagnosis and decrease the chances of recovery after surgical evacuation. The neurologist should contact the anesthesiologist to clarify the anesthetic approach used, the effects of the drugs administered, and the expectation of the duration of their effect. In the acute phase, it may be difficult to differentiate between a compressive epidural hematoma and spinal cord ischemia. Preservation of posterior column sensation is expected with an anterior spinal artery infarction. Spinal CT scan allows visualization of the hematoma in most cases, but its sensitivity is suboptimal

TABLE 55-3 ■ Complications Attributed to Spinal or Epidural Block by Patients and Legal Advisers and Reported to Swedish Patient Insurance Database During 1980–1984

	Type of Anesthesia			
Complication	Epidural Block	Intrathecal Block	Caudal Block	Block and General Anesthesia in Combination
Death	1	—	—	—
Brain damage	1	—	—	1
Symptoms of cauda equina lesions	12	20	2	5
Spinal/epidural hematoma	2	—	—	—
Subdural hematoma	—	2	—	—
Subarachnoid hemorrhage	1	—	—	—
Significant paresis	10	7	—	—
Purulent meningitis	—	2	—	—
Deep local infection	—	1	—	—
Somatosensory disturbances	18	21	—	4
Chronic back pain	7	8	1	2

From Puke M, Arnér S, Norlander O: Complications of regional anaesthesia, with special reference to epidural, spinal and caudal anaesthesia. p. 1106. In Nunn JF, Utting JE, Brown BR Jr (eds): General Anaesthesia. 5th Ed. Butterworth, London, 1989, with permission.

when hardware is present. Therefore, MRI of the spine should be obtained urgently if possible. Urgent surgical evacuation of the hematoma may result in excellent functional recovery.

The American Society of Regional Anesthesia and Pain Medicine has published recommendations for the management of patients receiving antithrombotics who require regional anesthesia.[8] Warfarin should be discontinued 5 days before planned regional anesthesia, and anticoagulation with warfarin should be reversed until the international normalized ratio is 1.5 or less before urgent interventions. Patients at high risk of thromboembolism should receive bridging with unfractionated heparin (to be stopped 4 hours before surgery) or low-molecular-weight heparin (reduced to half of the usual daily dose and stopped 24 hours before surgery). After surgery, warfarin can be resumed on the first day and heparin products restarted after 24 hours following minor surgeries or 48 to 72 hours after major surgeries. Although continuation of aspirin is acceptable if necessary, clopidogrel should be discontinued 5 to 10 days before the surgery and can be restarted 24 hours after it. It is recommendable to discontinue dabigatran 5 days before the procedure, although 3 days may be an acceptable interval in patients with creatinine clearance greater than or equal to 80 mL/min. Dabigatran should not be restarted until at least 6 hours following removal of the neuraxial catheter. The factor Xa inhibitors rivaroxaban and apixaban should be discontinued 3 days before the intervention and not restarted until at least 6 hours after removal of the neuraxial catheter. Neuroaxial blocks are discouraged in patients with severe impairment of renal function (creatinine clearance ≤ 30 mL/min).

Epidural abscess can also cause postoperative paraparesis, but its presentation is usually delayed (at least for days after surgery), and cases exclusively related to neuroaxial blockade are rare (Table 55-4).

TABLE 55-4 ■ **Patterns of Onset and Resolution of Four Neurologic Syndromes Occurring in Rare Patients Following Spinal or Epidural Block**

Neurologic Syndrome	Onset of Symptoms	Resolution of Symptoms
Aseptic meningitis	<24 h	<7–10 days
Cauda equina syndrome	Immediate or several days' delay	Permanent or temporary
Adhesive arachnoiditis	Weeks after block	Permanent
Epidural abscess	Days to months after block	Permanent or temporary

Neuropathy

The incidence of neuropathy has been estimated to be less than 0.04 percent after neuroaxial blockade and less than 3 percent following peripheral blockade, although these rates should be considered general approximations.[9] Neurologic symptoms and deficits are typically transient. Although prospective studies with blinded assessment are lacking, persistent postoperative neuropathy after regional anesthesia is quite infrequent.

Neuropathies can occur due to various mechanisms, some of which are not strictly related to anesthesia. Mechanical stress from stretch or compression of nerves as a result of malpositioning during surgery is a common cause; neuropathies are more likely to occur after prolonged surgeries. Other risk factors include male sex, diabetes mellitus, smoking, hypertension, vascular disease, obesity or extremely thin body habitus, and pre-existing clinical or subclinical nerve dysfunction. Some of these associations suggest that ischemic and metabolic insults play a role in pathogenesis.

The most frequently affected nerves in the upper extremities are the ulnar nerve and brachial plexus and in the lower extremities the sciatic, femoral, and fibular (peroneal) nerves and the lumbosacral plexus.[9] The predisposition of these particular nerves probably relates to their susceptibility to stretch and compression. The most common deficits that result are pure sensory and sensorimotor disturbances. Positioning strategies to reduce the risk of each of these peripheral neuropathies have been

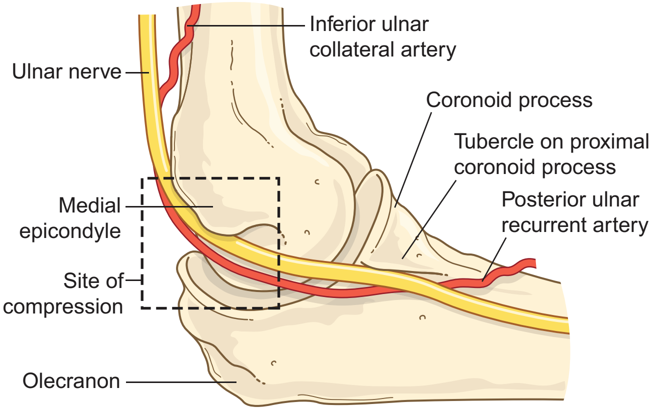
Inferior ulnar collateral artery
Ulnar nerve
Coronoid process
Tubercle on proximal coronoid process
Posterior ulnar recurrent artery
Medial epicondyle
Site of compression
Olecranon

FIGURE 55-1 ■ Typical anatomic site of ulnar nerve compression during surgery.

described.[10] Avoidance of arm abduction beyond 90 degrees in supine patients diminishes stretch of the brachial plexus. Minimizing pressure over the ulnar groove, avoidance of excessive flexion of the elbow (Fig. 55-1), and use of protective elbow padding are recommended to reduce ulnar nerve injuries. Restricting stretch of the hamstring muscle and the degree of hip flexion when the patient is in the lithotomy position lessens the risk of sciatic neuropathy. Perioperative fibular (peroneal) neuropathies can be averted through careful avoidance of prolonged pressure over the fibular head and the use of protective padding. Limb position and external compression play a lesser role in the pathogenesis of perioperative femoral neuropathies, which are attributed most often to damage from inappropriate retractor placement or pelvic hematoma (Fig. 55-2).

Cauda equina syndrome is a rare complication of spinal anesthesia, attributed speculatively to maldistribution of the local anesthetic into the subarachnoid space. Most reported cases have occurred after continuous spinal anesthesia, and the predominant manifestations are localized to the S1 nerve roots, presumably because of their more posterior location.

Full recovery from these neuropathies is often seen after days to weeks, but some patients suffer persistent disability. There is insufficient information to guide prognostication, except that electrodiagnostic evidence of demyelination (conduction block) rather than axonal loss implies a better prognosis than otherwise.

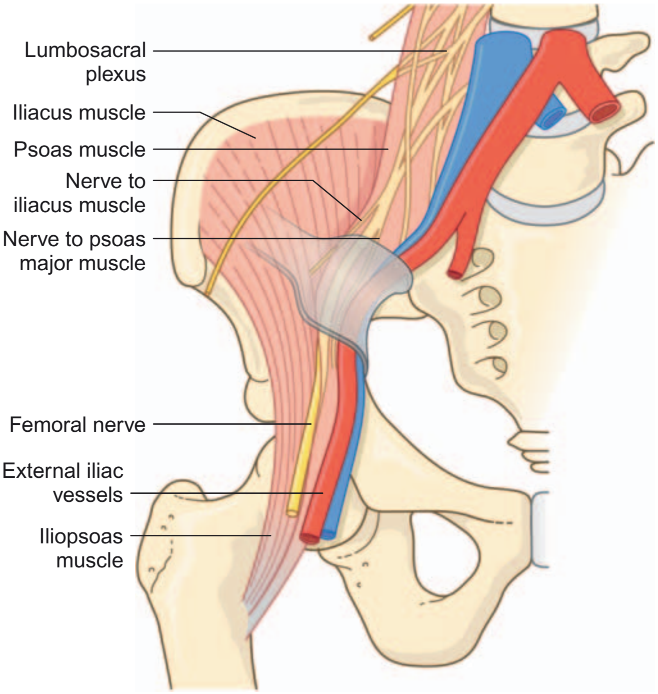

FIGURE 55-2 ■ Illustration of the common mechanism of compression of the femoral nerve through pressure applied with the surgical separator.

Transient Neurologic Symptoms

A syndrome known to anesthesiologists as *transient neurologic symptoms* is characterized by early postoperative pain in the buttocks and legs after spinal anesthesia. The pain, which may be severe, typically develops after an initial asymptomatic period of a few hours and is frequently bilateral. The syndrome resolves spontaneously within 2 to 5 days. The risk of this complication is higher with lidocaine and mepivacaine than with other local anesthetics and is not influenced by the dose or concentration of the drug.[10] The main differential diagnoses include cauda equina syndrome, aseptic meningitis, adhesive arachnoiditis, and epidural hematoma or abscess. Imaging reveals no structural abnormality that can explain the symptoms, and the etiology remains uncertain.

Visual Loss

Posterior ischemic optic neuropathy is a rare complication of complex spine surgeries that require prolonged prone positioning, associated with intraoperative blood loss and hemodynamic instability.[11] The performance of staged surgeries, a more liberal intraoperative transfusion strategy, avoidance of intraoperative hypotension, and maintenance of the head at or above the level of the heart have each been recommended, but the etiology of the condition is unclear and the value of these strategies is unproven. Although the visual impairment can be transient, it is often severe and bilateral and may be permanent. Cardiac surgeries also may be complicated in rare instances by visual loss, typically due to anterior ischemic optic neuropathy or retinal embolism. Anesthesia technique does not appear to be associated with the risk of this type of perioperative visual loss.[11]

Hearing Loss

Ear blockage may occur after general anesthesia with nitrous oxide in patients susceptible to Eustachian tube obstruction. Presumably mucosal edema facilitates the development of the condition. Prognosis is favorable, with resolution over hours to a few days.

Transient hypoacusis, typically subtle, may follow spinal anesthesia. The proposed mechanism is a decrease in cerebrospinal fluid volume reducing perilymphatic pressure and leading to endolymphatic hydrops. The hypoacusis is frequently, but not always, associated with headache. Use of smaller-diameter spinal needles may reduce the risk.

Cranial Nerve Palsies

Abducens nerve palsy has been described after spinal anesthesia, and it can be unilateral or, rarely, bilateral. Typically accompanied by positional headache, it occurs in cases with substantial cerebrospinal fluid loss. The risk is related to the diameter of the spinal needle.

Pupillary changes may follow neuroaxial blocks. Horner syndrome sometimes occurs after epidural anesthesia, typically after labor; the condition lasts only for the duration of the anesthetic block. It can also occur transiently after brachial plexus blockade. Anisocoria found after surgery should not be attributed to anesthetic blockade except when the patient is fully lucid and the examination clearly reveals an isolated Horner syndrome.

Bilateral pupillary dilatation in the immediate perioperative period may be caused by “total” spinal anesthesia, a condition provoked by the unintentional injection of the anesthetic drug into the subarachnoid space. Marked mydriasis and unconsciousness are common, and the problem is typically recognized in the operating room.

Exceptional cases of unilateral and transient trigeminal and facial nerve dysfunction have also been reported after epidural anesthesia for women in labor.

PERIOPERATIVE RIGIDITY

The differential diagnosis of a febrile and rigid patient includes serotonin syndrome, neuroleptic malignant syndrome, and malignant hyperthermia. Serotonin syndrome is most common in the postoperative period, and any patient receiving serotonergic drugs, especially in combination, is at risk for this disorder. Commonly used serotonergic medications include antidepressants, mood stabilizers, antihistamines, triptans, muscle relaxants, and amphetamines, and those prescribed frequently after surgery include opiates (particularly fentanyl), tramadol, and antiemetics. Diagnosis is based on the presence of alterations in consciousness (sometimes with agitation), signs of neuromuscular irritability (hyperreflexia, clonus, rigidity, tremors, myoclonus), and features of autonomic instability (fever, tachycardia, hypertension, diaphoresis). Patients often have mydriasis and hyperactive bowel sounds with diarrhea. The predominance of the rigidity in the lower limbs compared with the upper limbs is distinctive. In severe cases, pronounced rigidity is associated with fever and muscle injury. Recovery follows prompt discontinuation of all serotonergic drugs, usually over hours to days. Cyproheptadine or chlorpromazine might accelerate recovery in more severe cases. Induced neuromuscular paralysis may be necessary in patients with extreme rigidity, fever, and rhabdomyolysis.

The neuroleptic malignant syndrome is uncommon. It presents 1 to 3 days after exposure to an antidopaminergic drug, with clinical features that include extreme rigidity, fever, dysautonomia, and an elevated serum creatine kinase level. Bradykinesia, lead-pipe rigidity without leg predominance, hyporeflexia, and normal bowel sounds distinguish it from the serotonin syndrome. When the diagnosis of neuroleptic malignant syndrome is suspected, antidopaminergic medications should be stopped and patients should be monitored for dysautonomic complications. Bromocriptine, a dopamine agonist, may diminish the rigidity; severe cases are treated with dantrolene, a potent muscle relaxant.

Malignant hyperthermia occurs in the operating room upon anesthesia induction and neuromuscular paralysis, or within minutes of anesthesia cessation. It is caused by mutations affecting receptors that control the transport of calcium from the sarcoplasmic reticulum to the cytoplasm. Exposure to inhalational anesthetics, especially when succinylcholine is administered, results in excessive availability of calcium in the cytoplasm which, in turn, provokes sustained muscle contraction. A hypermetabolic crisis follows, manifest by hypercapnia, hyperthermia, and mixed acidosis. Severe rhabdomyolysis and cardiac arrhythmias may occur if the diagnosis is delayed. Immediate discontinuation of the anesthetic agent and administration of dantrolene are extremely effective in reversing the syndrome.

PERIOPERATIVE SEIZURES

Surgery—with the exception of neurosurgery—does not predispose to seizures in general. Some anesthetics have antiepileptic properties while others lower the seizure threshold (Table 55-5). Seizures following anesthesia are uncommon overall. Risk factors include a history of epilepsy (especially in children), previous structural brain injury, and substance abuse.

When postoperative seizures occur in patients with epilepsy, they are generally related to poor preoperative control of the epilepsy and not to the anesthetic.[12] In patients with epilepsy, drugs known to lower the seizure threshold should be avoided. Epileptic seizures should

TABLE 55-5 ■ Anesthetics and Analgesics Reported to Cause or Suppress Seizure Activity in Humans

Proconvulsants	*Anticonvulsants*
Nitrous oxide	Halothane
Halothane	Enflurane
Enflurane	Isoflurane
Isoflurane	Thiopental
Morphine	Etomidate
Meperidine	Diazepam
Fentanyl	Lorazepam
Sufentanil	Midazolam
Methohexital	Ketamine
Etomidate	Propofol
Diazepam	Local anesthetics
Ketamine	
Propofol	
Local anesthetics	

From Modica PA, Tempelhoff R, White PF: Pro- and anticonvulsant effects of anesthetics. Part 1. Anesth Analg 70:303, 1990.

be differentiated from seizure-like movements (including myoclonus, often seen upon propofol withdrawal) and psychogenic nonepileptic seizures.

Postoperative seizures in patients without a history of epilepsy should lead to evaluation for a structural brain lesion, such as an acute stroke, more commonly seen after cardiovascular surgery. Old cortical strokes may also serve as a substrate for postoperative seizures, usually occurring with some delay after the surgery and not precipitated by anesthesia itself.

Postcraniotomy seizures are more frequent and vary depending on the type of surgery. Seizures can even occur, albeit rarely, after operations in the posterior fossa. The value of prophylactic antiseizure medications is unclear.

PERIOPERATIVE HEADACHE

TABLE 55-6 ■ Causes of Perioperative Headache

- Exacerbation of pre-existent primary headache disorder
- Myofascial headache
- Caffeine withdrawal
- Postdural puncture headache
- Closed air-space headache (e.g., effects of nitrous oxide on inflamed sinus or middle ear)
- Trigeminal branch neuropathy
- Structural intracranial lesion
- CNS infection

Although there are many causes of postoperative headache (Table 55-6), those most directly related to anesthesia follow regional anesthesia. Dural puncture can cause a persistent leak of cerebrospinal fluid and the ensuing intracranial hypotension classically manifests with orthostatic headaches (i.e., they are worsened when the patient is upright and ameliorated by recumbency). This complication is more common in thin young women, and it sometimes occurs in obstetric patients when inadvertent dural puncture occurs during epidural anesthesia. Use of smaller needle size and good technique (e.g., bevel inserted parallel to the plane of the dural fibers, use of a single pass) decrease the incidence of this complication.

An arbitrary period of recumbency following dural puncture does not decrease the incidence of headache, and early ambulation may actually be preferable. Caffeine is often recommended for treatment and seems to work in practice but its value, or that of nonsteroidal anti-inflammatory agents, has not been demonstrated conclusively. Morphine, cosyntropin, and aminophylline are the agents best supported by evidence of efficacy, but they are rarely prescribed for the headaches that follow dural puncture.[13] Epidural blood patch is the best treatment for this type of headache, and it is effective in more than three-quarters of patients. Its efficacy may be lower if placed more than 4 days after the puncture.

Another cause of headache directly related to anesthesia is sinus or middle ear block in patients receiving nitrous oxide. As the gas equilibrates with the air contained in these cavities, pressure may mount in patients with mucosal inflammation.

Compression of the supraorbital or infraorbital branches of the trigeminal nerve from a tight face mask used during anesthesia may also be a rare cause of severe headache after surgery.

ANESTHESIA IN PATIENTS WITH NEUROLOGIC DISEASE

Neurologists are often asked by patients with chronic neurologic disease or their families whether exposure to anesthesia during surgery can exacerbate their underlying condition. The answer depends on the disease in question, the type of surgery, and the condition of the patient.

There are no studies comparing the safety of regional to general anesthesia in patients with pre-existing neurologic disease. It has been postulated that techniques of regional anesthesia may exacerbate previous peripheral neurologic injury by inducing a secondary insult, particularly in patients with pre-existing neuropathies. However, the results from most studies indicate that anesthesia can generally be used safely in patients with various neurologic diseases.

Alzheimer Disease

Anesthetic drugs, especially inhalational agents, have the potential to induce or accelerate the neurodegenerative changes characteristic of Alzheimer disease.[14] Potential mechanisms include neuronal calcium dysregulation, increased amyloid beta production and aggregation, increased tau phosphorylation, and activation of apoptotic pathways in the predisposed brain exposed to isoflurane. The evidence for these effects comes from experimental models, and there is no conclusive clinical data associating anesthetic exposure with a greater risk of Alzheimer disease; indeed, some epidemiologic studies appear to refute any such association. Various anesthetic gases may have different effects. Isoflurane, but not desflurane, has been associated with an increase in Aβ40 protein levels in human cerebrospinal fluid 24 hours after surgery compared with control patients undergoing spinal anesthesia.

Many general anesthetics decrease central acetylcholine release and depress cholinergic transmission in the basal forebrain, a condition that mimics changes found in Alzheimer disease. Most anesthetic agents also interact with muscarinic and nicotinic receptors in the brain, typically in a dose-dependent manner. Propofol and remifentanil interfere less with cholinergic function than inhalational drugs and other opioids.

Observational studies indicate that presurgical cognitive impairment and dementia are associated with postoperative cognitive decline, poor functional recovery, and an increased risk of death. Whether adjustments in the anesthetic regimen (such as the use of propofol instead of inhalational agents) can decrease this risk remains unclear. Hypnotics, opioids, inhalational drugs, and neuromuscular blocking agents produce more variable responses with advanced age and should be used prudently in patients with documented cognitive impairment.

Parkinson Disease

For patients with Parkinson disease who require surgery, the main problem relates to transient discontinuation of their antiparkinsonian regimen. These medications should be continued to as close to the beginning of anesthesia as possible, and restarted as soon after surgery as feasible to minimize parkinsonian complications. In prolonged surgeries, intraoperative administration of levodopa via a nasogastric tube can be considered. During the early postoperative period, patients with Parkinson disease have an increased risk of postextubation respiratory failure and aspiration pneumonia due to upper airway dysfunction, as well as hemodynamic instability from impairment of autonomic control. Delirium is also common postoperatively in patients with Parkinson disease.

Succinylcholine may be unsafe in patients with Parkinson disease who are very rigid because of an increased risk of inducing severe hyperkalemia; nondepolarizing muscle relaxants can be used safely instead. Propofol is generally the preferred induction agent for these patients. Inhalational anesthetics should be administered cautiously due to a greater risk of inducing hypotension and cardiac arrhythmia. Ketamine use may be associated with an excessive sympathetic response. Thiopental can theoretically decrease striatal dopamine release, but is probably safe.

Antidopaminergic drugs should be avoided, including various antiemetics commonly prescribed in the recovery room (e.g., droperidol, metoclopramide). Meperidine should not be used in patients who have taken selegiline or rasagiline in the preceding 2 weeks because this combination can result in severe hypertension or hypotension, respiratory depression, convulsions, malignant hyperthermia, excitation, peripheral vascular collapse, coma, and death. Tramadol, methadone, tapentadol, and propoxyphene must also be avoided for the same reason. When fentanyl is administered, greater rigidity can be expected, and occasionally opioids of all types can cause severe acute dystonia responsive to naloxone.

Functional neurosurgery (deep brain stimulation) for the treatment of Parkinson disease represents a particular challenge because—depending on technique—patients are kept awake to allow for adequate monitoring and targeting of deep brain structures during lead insertion. The advantages of awake craniotomy need to be balanced against the risk of operative complications such as intracranial hemorrhage, which may increase when patients are uncomfortable and not fully cooperative. When trying to preserve patient cooperation, dexmedetomidine can be helpful in providing mild sedation. Propofol is also a good agent as it does not affect electrophysiologic monitoring.

Epilepsy

The risk of perioperative seizures is very small in patients with epilepsy undergoing general anesthesia, and epileptic patients do not appear to have an increased risk of other perioperative adverse effects. Children with epilepsy may be more susceptible than adults to develop seizures associated with anesthesia. Regional blockade can be performed safely.

Many anesthetic agents produce complex effects on brain electrical activity and may have proconvulsant and anticonvulsant properties depending on the dose and concentration (Table 55-5). Although most anesthetic regimens are safe for patients with epilepsy, some agents should be used cautiously because of their proconvulsant potential at usual doses, including etomidate and intravenous lidocaine. Sevoflurane is more epileptogenic than the other inhaled anesthetics, and short-acting opioids (e.g., alfentanil, sulfentanil, remifentanil) increase epileptiform activity during intraoperative electrocorticography for epilepsy surgery. Propofol, barbiturates, benzodiazepines, and other volatile agents (especially isoflurane and desflurane) conversely have antiepileptic effects and are the preferred options in patients with epilepsy.

Other Chronic Diseases of the Central Nervous System

Patients with multiple system atrophy and an accompanying dysautonomia may develop dangerous hemodynamic instability in the perioperative period. General anesthesia can be used safely in these patients, but agents that lead to hypotension should be avoided; spinal anesthesia may be preferable.

Patients with amyotrophic lateral sclerosis are particularly susceptible to the effects of muscle relaxants. Succinylcholine should be avoided in all patients with severe neuromuscular disease because it can induce hyperkalemia. When muscle relaxation is deemed indispensable, nondepolarizing blocking agents should be administered in low doses using nerve stimulator monitoring. A regimen of propofol and remifentanil without muscle relaxation is safe in these patients. In patients with amyotrophic lateral sclerosis requiring gastrostomy tube placement, opiates may decrease the ventilatory drive, precipitating respiratory failure.

Worsening myelopathic symptoms following spinal anesthesia have been reported rarely in patients with multiple sclerosis or other demyelinating conditions, but a large case series of patients with multiple sclerosis, amyotrophic lateral sclerosis, and postpolio syndrome revealed no instances of severe exacerbation of preoperative neurologic deficits after spinal or epidural anesthesia.

Patients with Huntington disease may need closer monitoring due to their hyperkinetic movement disorder, but can generally receive anesthesia safely. Responses to muscle relaxants, induction agents, volatile anesthetics, benzodiazepines, and opioids are usually normal.

Neuromuscular Disorders

Severe neurologic complications are rare in patients with diabetic and nondiabetic peripheral neuropathy who undergo surgery using regional anesthesia. The risk of cauda equina syndrome may be increased in patients with spinal stenosis.

The surgical planning of patients with myasthenia gravis should incorporate input from the treating neurologist. Preoperative treatment with plasma exchange or intravenous immunoglobulin can reduce the risk of postoperative myasthenic crisis. After surgery, early weaning from mechanical ventilation and prompt reinstitution of aceylcholinesterase inhibitors are advisable. Various medications may worsen myasthenia gravis, including muscle relaxants and certain antibiotics such as the aminoglycosides.

The risk of malignant hyperthermia may be increased in patients with muscular dystrophies, although the degree of this risk is not well defined. Succinylcholine is contraindicated in patients with muscular dystrophies and metabolic myopathies because of the danger of life-threatening hyperkalemia and rhabdomyolysis.

ANESTHESIA IN THE NEUROCRITICAL CARE UNIT

Anesthetic drugs are commonly prescribed in the intensive care unit (ICU) for sedation, control of intracranial hypertension, and treatment of refractory seizures. The prolonged administration and high doses used for some of these indications may provoke complications not encountered with regular perioperative use.

Prolonged sedation in the ICU is associated with a greater incidence of delirium. Daily sedative interruption in patients receiving mechanical ventilation decreases the duration of mechanical ventilation and length of stay in the ICU. This practice should be combined with daily monitoring for signs of delirium employing validated scores, such as the Confusion Assessment Method for the intensive care unit (CAM-ICU). Dexmedetomidine, a central α_2-agonist, is associated with reduced rates of delirium when compared with benzodiazepines such as midazolam.[15]

Propofol infusion syndrome is a potentially life-threatening complication caused by the prolonged administration of high doses of this drug (usually exceeding 4 to 5 mg/kg per hour for more than 48 hours). Initially recognized in children, who appear to be at higher risk, it also can occur in adults and presents with lactic acidosis, rhabdomyolysis, hyperlipidemia, hyperkalemia, renal failure, and refractory bradycardia with cardiac failure. In the most severe cases, cardiac arrest may occur. Uncoupling of the respiratory chain causing impaired mitochondrial free fatty acid metabolism is involved in the pathogenesis of this disorder. Propofol infusion syndrome has been reported during the treatment of refractory status epilepticus and in severe traumatic brain injury patients with refractory intracranial hypertension. Since other options exist for control of refractory seizures or recalcitrant intracranial hypertension, it is advisable to avoid using large doses of propofol for these indications.

Patients with prolonged refractory status epilepticus are commonly treated with anesthetics. Options include midazolam, propofol, ketamine, barbiturates, and less commonly inhalational anesthetics such as isoflurane. Midazolam is safe and effective, but tachyphylaxis develops over time. Continuous infusion of high-dose lorazepam may produce severe acidosis from propylene glycol toxicity and therefore its use should be discouraged. Ketamine, an *N*-methyl-D-aspartate antagonist, can be very useful when started early and used in adequate doses. Barbiturates are highly effective, but almost invariably associated with complications, including hypotension from myocardial depression, ileus, hepatotoxicity, and increased susceptibility to infections (particularly pneumonia). Isoflurane can be effective in aborting seizures, but may induce neurotoxicity with prolonged use.

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SECTION

15

Critical Illness and General Medical Disorders

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CHAPTER

56

Neurologic Complications in Critically Ill Patients

JOHN A. MORREN ■ EDWARD M. MANNO

SEPSIS-ASSOCIATED ENCEPHALOPATHY
- Epidemiology
- Overview of the Mechanisms of Sepsis
- Pathogenesis of the Encephalopathy
- Presentation and Evaluation
- Long-Term Effects of Sepsis-Associated Encephalopathy
- Management and Future Studies

NEUROMUSCULAR CONDITIONS IN CRITICALLY ILL PATIENTS
- Disorders of Nerve
  - *Critical Illness Polyneuropathy*
  - *Motor Neuropathy and Neuromuscular Blocking Agents*
  - *Chronic Polyneuropathies*
- Neuromuscular Junction Transmission Disorders and Myopathies
  - *Transient Neuromuscular Junction Blockade*
  - *Critical Illness Myopathy*
  - *Thick-Filament Myosin Loss*
  - *Rhabdomyolysis*
  - *Acute Necrotizing Myopathy of Intensive Care*
  - *Cachectic Myopathy*
- Co-existing Critical Illness Polyneuropathy and Myopathy

CONCLUDING COMMENTS

Injury to other organ systems may have a direct or remote effect on the neurologic system. Hepatic, cardiac, pancreatic, and renal dysfunction can directly affect neurologic transmission and function through a variety of mechanisms. This chapter will examine what is currently understood about the immediate and long-term effects of critical illness on both the central and peripheral nervous systems. Methods to examine, prognosticate, and potentially treat these processes are important for all clinicians.

SEPSIS-ASSOCIATED ENCEPHALOPATHY

Septic encephalopathy is a nebulous term used to describe the encephalopathy encountered in the critically ill patient. It excludes patients that have direct neurologic injury, indirect effects of other failing organ systems, or exogenous toxins. Thus, it is a diagnosis of exclusion. The terminology itself is confusing since sepsis is common but is not necessary for the diagnosis. Historically defined as "altered brain function due to the presence of microorganisms or toxins in the blood," this definition is not entirely accurate since bacteria are not often identified and exogenous substances are excluded from the definition. Sepsis-associated encephalopathy has now been generally accepted as the most appropriate terminology.[1]

Epidemiology

Sepsis is common and accounts for the majority of deaths in an intensive care unit. Mortality remains high despite recent advances in treatment. The encephalopathy associated with sepsis has an even worse prognosis. Studies report up to 71 percent of critically ill patients develop an encephalopathy. The presence and severity of the encephalopathy have significant impact on both immediate mortality and long-term cognitive capabilities.[2]

Overview of the Mechanisms of Sepsis

A response to an infection is initiated when pattern-recognizing receptors on macrophages bind cellular components of microbial cell walls. Binding of these receptors initiates a signaling cascade, via the nuclear factor−κβ system, to release cytosolic factors which translocate to the nucleus. These translocated factors

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activate gene transcription for proinflammatory cytokines [tumor necrosis factor (TNF), and interleukin-1 (IL-1)], chemokines, intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion molecule 1, and nitric oxide. These activated factors subsequently attract polymorphonuclear leukocytes (PMNs) to the site of the injury. PMNs release local substances which account for the changes seen with inflammation (erythema, edema, warmth).[3]

Inflammation is then regulated through a balance between proinflammatory cytokines released by macrophages and anti-inflammatory factors released by PMNs. This balance typically will contain an infection locally. Sepsis occurs when the response to an infection generalizes beyond local boundaries to affect remote organ systems. The systemic inflammatory response syndrome (SIRS) reflects a similar process that is not initiated by an acute infection. Systemic release of proinflammatory cytokines, predominantly IL-1 and TNF, can become self-sustaining, leading to systemic inflammation, complement activation, and stimulation of both coagulation and fibrinolytic cascades. All of the above substances and features have been shown to be extensively involved in the development of sepsis and multiorgan failure in multiple animal models. Various single-nucleotide polymorphisms have been demonstrated to increase genetic susceptibility to sepsis.

Sepsis affects all organ systems primarily through its effect on the endothelium of vascular tissues. Sepsis induces both vasodilation (most likely through nitric oxide) and myocardial depression, leading to significant hypotension. Regional circulation is altered, affecting appropriate distribution to ischemic organs. Endothelial dysfunction leads to increased vascular permeability with subsequent tissue edema. Decreased functional capillaries at the microcirculatory level may be due to extrinsic compression from tissue edema or secondary to intravascular coagulation. Red cell deformability is decreased in sepsis, which further inhibits oxygen delivery.[3]

Oxygen utilization at the mitochondrial level is directly affected by proinflammatory mediators which cause direct mitochondrial dysfunction, most likely through direct inhibition of respiratory chain enzymatic function. Oxidative stress damage is believed to account for an increase in mitochondrial breakdown products. Direct cell death may therefore be attributed to cellular inability to utilize oxygen. Secondary cell death through apoptosis is typically decreased in sepsis. The net effect however may be to worsen apoptosis as septic mediators and proinflammatory cytokines delay apoptosis in macrophages and neutrophils.[3]

Pathogenesis of the Encephalopathy

The endothelial and microvascular effect of sepsis affects all organs. Subsequent hypoxia from pulmonary fibrosis, uremia from renal failure, or alterations in amino acid metabolism from hepatic failure, all may contribute to the encephalopathy commonly encountered in septic patients. However, an encephalopathy can develop early in the course of sepsis or SIRS prior to the development of the effects of secondary organ failure. While the exact source and mechanism of how neurologic dysfunction occurs with inflammation is unknown, it is generally believed that septic mediators, primarily proinflammatory cytokines and complement factors, gain access to the brain neuropil leading to functional disruption of neurologic transmission and eventual cell damage and death.

How these factors gain access to the brain has been an area of considerable study. Animal experiments have supported a direct toxic effect of some mediators to the integrity of the blood–brain barrier (BBB). Neonatal kittens exposed to *Escherichia coli* lipopolysaccharide develop diffuse cerebral white matter disruption with noted extravasation of Evans blue dye throughout the brain. Similarly, horseradish peroxidase is transported retrograde into septic rat neuropil demonstrating a patchy disruption of the BBB.[3,4] More recently, lipopolysaccharide exposures have been linked to direct transport of cytokines across the BBB. Inflammatory mediators may also gain direct access to the brain through the circumventricular organs located around the midline ventricular system.

However, the exact factors that increase BBB permeability are unknown. Proinflammatory molecules are increased in patients with septic-associated encephalopathy and increase the permeability of endothelial cells through pinocytosis. The loss of BBB integrity leads to perimicrovascular edema with disruption of astrocytic end feet. Similar findings have been reported with complement activation and inflammatory cytokines. Evidence from murine models implicate TNF, anaphylaxin C5a, and the cytokines IL-6 and IL-1b as mediators of BBB disruption. ICAM is increased on microvessels in sepsis and mediates adherence and entry of leukocytes into the brain.[4]

Once inflammatory mediators have gained access to the brain parenchyma, the results of these septic mediators are similar to their effects on other organs. Activated leukocytes generate free radicals that react with erythrocyte membranes causing increased swelling. This process can lead to cerebral hypoperfusion and may contribute to the encephalopathy. Inflammatory mediators in the brain as in other organs may impair oxygen extraction, utilization, or both at the mitochondrial level. Thus decreased cerebral blood flow in sepsis may be an expected response to decreased cerebral metabolism.

Cerebral ischemia itself, however, does appear to be present in sepsis. Dead neurons have been identified in septic pigs with maintained cerebral perfusion, and microvascular lesions are commonly found on imaging and pathology. Brain apoptosis in sepsis has been documented in exposure to lipopolysaccharide, presumably due to mitochondrial dysfunction.[4] Postmortem studies have shown inducible nitric oxide synthase leadng to neural apoptosis in the hippocampus and cardiovascular centers.[4] Neuronal damage is most evident in the highly metabolic neurons of the hippocampus.

An increased production of nitric oxide has also been postulated to contribute to the development of the encephalopathy. In several animal models, tumor necrosis factors increase the formation of intracellular nitric oxide. While the exact mechanism is unknown, several putative mechanisms involve the release of glutamate from both neurons and astrocytes, leading to excitotoxic death mediated through *N*-methyl-D-aspartate (NMDA) receptors; NMDA receptor blockade has limited the long-term cerebral effects of sepsis in animal models. Nitric oxide may also alter cerebral blood flow and metabolism and coupling as it is also an inhibitor of mitochondrial respiration. Neurotransmission is also impacted in septic-associated encephalopathy. Altered levels of amino acid neurotransmitters have been reported in the rat model of sepsis. Disrupted glutamate transmission appears to be particularly involved.

The parasympathetic and sympathetic nervous system also may play a role in the development of the encephalopathy. Parasympathetic activity may in part mediate the inflammatory response as increased vagal tone appears to decrease inflammation and improve mortality. Similarly, adrenergic activation appears to produce an anti-inflammatory effect which may be neuroprotective.[4]

Presentation and Evaluation

The encephalopathy associated with sepsis and inflammation may present acutely or subtly with a slow progression. Disorientation, impaired cognition, and inattentiveness can progress to agitation, delirium, stupor, and coma. Pupils are typically small and minimally reactive. Brainstem reflexes are generally maintained until late in the course. Focal signs are rare but can occur.[1]

The diagnosis remains one of exclusion. The patient should be evaluated for meningitis and infectious or autoimmune/paraneoplastic encephalitides. Similarly, encephalopathies secondary to failure of other organ systems (hepatic, renal, pulmonary, pancreatic) must be evaluated and treated if present. Failure of clearance and metabolism of the sedative medications commonly employed to treat critically ill patients can be delayed in multiorgan failure, thus complicating the evaluation. Cerebral hypoperfusion from cardiac failure can also contribute to encephalopathy.

Serum levels of neuron-specific enolase and S-100B are markers of neuronal and astrocytic damage. Both are increased with septic encephalopathy and correlate with worse outcome.[5] The electroencephalogram (EEG) can be normal but becomes slower, progressing from theta to delta activity and finally burst suppression as the encephalopathy worsens (Fig. 56-1).[6] Mortality similarly correlates with worse EEG findings. Nonconvulsive status epilepticus can occur and is probably under-recognized. Continuous EEG monitoring may be beneficial to demonstrate seizures and guide management. Magnetic resonance imaging (MRI) is sensitive to the changes that can occur during sepsis; microhemorrhages and small ischemic lesions are detected in approximately 10 percent of cases; white matter changes are common; and cortical atrophy is noted in long-term cases. Somatosensory evoked potentials, functional MRI, and positron emission tomography require more study as to their use in evaluating the encephalopathy associated with infection.

Long-Term Effects of Sepsis-Associated Encephalopathy

The long-term neurologic effects of sepsis have come under increasing scrutiny. Mild to moderate neurocognitive deficits have been reported consistently in septic patients and can be persistent. While recovery is possible in younger patients who are less severely affected, global cognitive impairment has been reported in 17 percent of patients evaluated 3 years postevent. Short-term memory appears to be particularly vulnerable. Analyses from long-term epidemiologic studies suggest that early dementia is twice as likely in patients who have an episode of sepsis.[7]

Management and Future Studies

There are no specific treatments for the encephalopathy associated with sepsis and inflammation. Early recognition and treatment of the underlying illness is the most effective therapy.

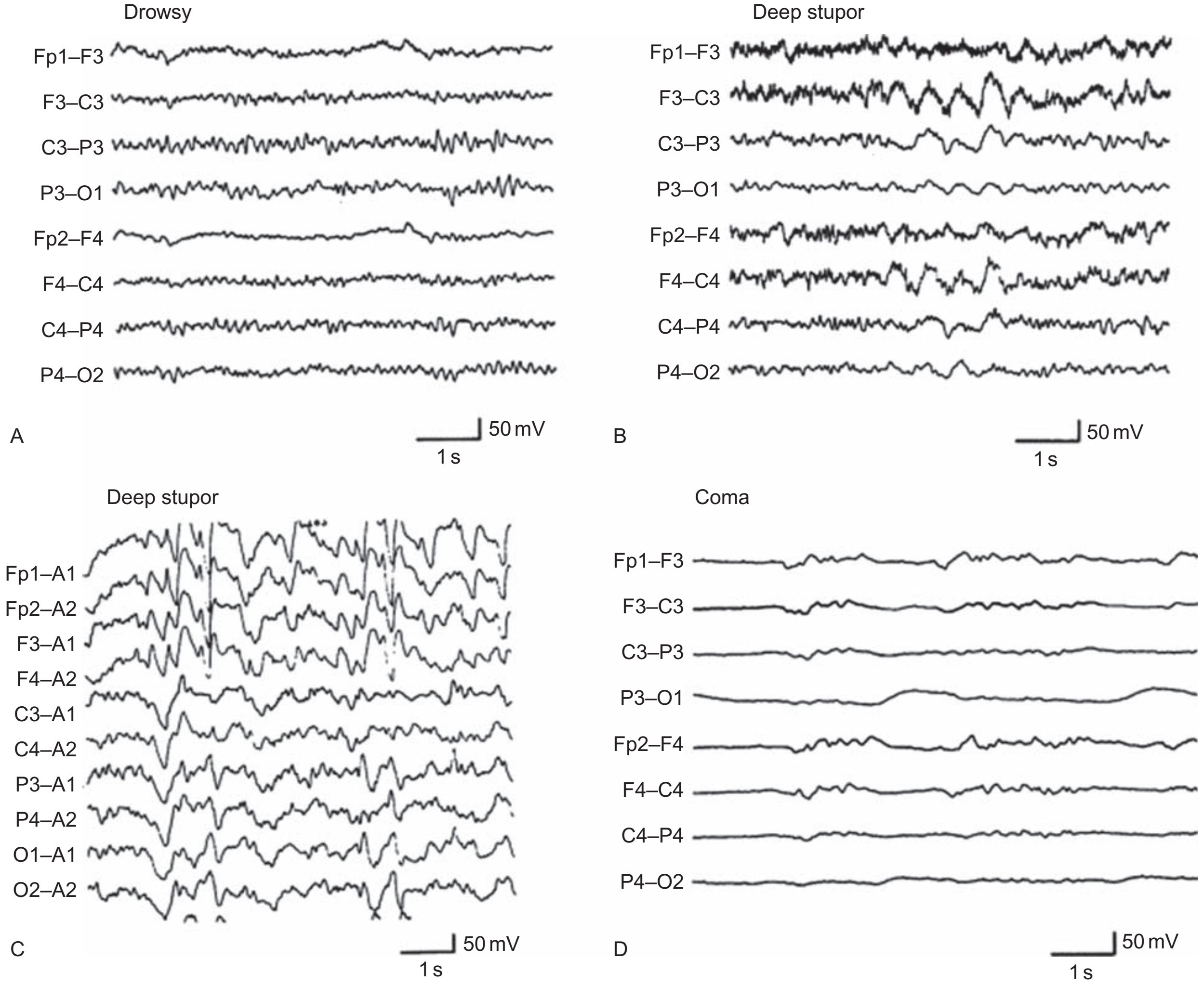
Drowsy
Fp1–F3
F3–C3
C3–P3
P3–O1
Fp2–F4
F4–C4
C4–P4
P4–O2
A
50 mV
1 s
Deep stupor
Fp1–F3
F3–C3
C3–P3
P3–O1
Fp2–F4
F4–C4
C4–P4
P4–O2
B
50 mV
1 s
Deep stupor
Fp1–A1
Fp2–A2
F3–A1
F4–A2
C3–A1
C4–A2
P3–A1
P4–A2
O1–A1
O2–A2
C
50 mV
1 s
Coma
Fp1–F3
F3–C3
C3–P3
P3–O1
Fp2–F4
F4–C4
C4–P4
P4–O2
D
50 mV
1 s

FIGURE 56-1 ■ Electroencephalograms (EEGs) from patients with septic encephalopathy. *A*, Patient with mild encephalopathy. The EEG shows a mild excess of low-voltage 6- to 7-Hz theta rhythms in both left (odd-numbered electrode placements) and right (even-numbered placements) hemispheres. *B to D*, Severely encephalopathic patients. *B*, Bilateral intermittent rhythmic delta (<3 Hz) waves on a background of mild slowing. *C*, Triphasic waves. *D*, Burst-suppression pattern. (From Bolton CF, Young GB: Neurological complications in critically ill patients. p. 981–997. In Aminoff MJ (ed): Neurology and General Medicine. 4th Ed. Churchill Livingstone Elsevier, Philadelphia, 2008, with permission.)

The multitude of inflammatory mediators that are believed to be involved in the development of the encephalopathy makes development of specific targets of treatment difficult. Inhibitors of nitric oxide synthase have been disappointing in animal studies.[8] Inhibitors of glutamate, antioxidants, and complement factors have shown promise, but their use in humans remains a future direction.[4]

NEUROMUSCULAR CONDITIONS IN CRITICALLY ILL PATIENTS

Critically ill patients may have neuromuscular dysfunction due to many possible etiologies that can affect the central as well as the peripheral nervous system (Table 56-1). This makes lesion localization particularly challenging to the clinician who is faced with multiple confounding features in the setting of critical illness. Compounding this difficulty is the frequent inability to obtain a history from the patient given mental state changes and physical impediments such as endotracheal tubes. In the modern ICU, the multiplicity of invasive lines, tubings, electrodes and wiring for monitoring equipment, limb splints, restraints, occlusive dressings, and bandages all represent formidable physical obstructions to the clinical examination that may otherwise be helpful in diagnosis.

Neuromuscular diagnoses are often delayed in critically ill patients due to the severity of their underlying

TABLE 56-1 ■ Differential Diagnosis of Neuromuscular Signs in Critically Ill Patients

Encephalopathy

Septic

Hypoxic-ischemic

Other

Myelopathy

Hypoxic-ischemic

Traumatic

Other

Neuropathy

Critical illness polyneuropathy

Thiamine deficiency

Vitamin E deficiency

Nonspecific nutritional deficiency

Pyridoxine abuse

Hypophosphatemia

Aminoglycoside toxicity

Penicillin toxicity

Guillain—Barré syndrome

Motor neuron disease

Porphyria

Carcinomatous polyneuropathy/polyradiculoneuropathy and paraneoplastic polyneuropathy/ganglionopathy

Compression neuropathy

Diphtheria

Neuromuscular Transmission Defects

Neuromuscular blocking agents

Aminoglycoside toxicity

Myasthenia gravis

Lambert—Eaton myasthenic syndrome

Hypocalcemia

Hypomagnesemia

Organophosphate poisoning

Wound botulism

Tick-bite paralysis

Myopathy

Critical illness (myosin-deficient) myopathy

Cachexia

Acute rhabdomyolysis

Acute necrotizing myopathy of intensive care

Electrolyte disturbances: potassium, phosphate, calcium, magnesium

Corticosteroid myopathy

Muscular dystrophy

Polymyositis and other inflammatory myopathies

Acid maltase deficiency

Adapted and modified from Bolton CF, Young GB: Neurological complications in critically ill patients. p. 981—997. In Aminoff MJ (ed): Neurology and General Medicine. 4th Ed. Churchill Livingstone Elsevier, Philadelphia, 2008, with permission.

or comorbid illnesses. Another complicating factor is that many primary critical care conditions will present with respiratory dysfunction and motor impairment, mimicking a primary neuromuscular illness.

Electrodiagnostic testing is often needed as part of the routine evaluation of critically ill patients with unexplained neuromuscular deficits. However, these investigations are significantly hampered by ICU factors including electrical interference, cool and edematous limbs, restricted access to sites of stimulation and recording due to physical barriers, and limited patient cooperation.

In making the diagnosis of critical illness weakness, the clinician should be diligent in excluding other conditions listed in Table 56-2. Fortunately, the more extensive use of electrodiagnostic testing has allowed for the sometimes fortuitous diagnosis of relatively uncommon neuromuscular conditions including Lambert—Eaton myasthenic syndrome and primary motor neuron disease, which may also be "unmasked" by intercurrent critical illness. More routinely, electrodiagnostic studies are ordered to support clinical diagnoses of more common conditions such as Guillain—Barré syndrome and myasthenia gravis.

Muscle biopsies are increasingly employed in critical care patients with clinical suspicion for myopathy and the need to distinguish between primary (e.g., dermatomyositis, polymyositis, metabolic, mitochondrial) and secondary (e.g., steroid- or statin-related) etiologies.

Phrenic nerve conduction studies and needle electrode examination of the diaphragm, with or without neuromuscular ultrasound, have proven useful in

TABLE 56-2 ■ Generalized Neuromuscular Conditions Associated With Critical Illness

Condition	Incidence	Clinical Features	Electrophysiologic Findings	Serum Creatine Kinase Level	Muscle Biopsy	Prognosis
Polyneuropathy						
Critical illness polyneuropathy	Common	Flaccid limbs and respiratory weakness	Axonal degeneration of motor and sensory fibers	Nearly normal	Denervation atrophy	Variable
Neuromuscular Transmission Defect						
Transient neuromuscular blockade	Common with neuromuscular blocking agents	Flaccid limbs and respiratory weakness	Abnormal repetitive nerve stimulation studies	Normal	Normal	Good
Critical Illness Myopathy						
Thick-filament myosin loss	Common with steroids, neuromuscular blocking agents, and sepsis	Flaccid limbs and respiratory weakness	Abnormal spontaneous activity	Mildly elevated	Loss of thick (myosin) filaments	Good
Rhabdomyolysis	Rare	Flaccid limbs	Near normal	Markedly elevated (myoglobinuria)	Normal or mild necrosis	Good
Necrotizing myopathy of intensive care	Rare	Flaccid weakness and myoglobinuria	Severe myopathy	Markedly elevated (myoglobinuria)	Marked necrosis	Poor
Disuse (cachectic) myopathy	Common	Muscle wasting	Normal	Normal	Normal or type II fiber atrophy	Good
Combined polyneuropathy and myopathy	Common	Flaccid limbs and respiratory weakness	Indicate combined polyneuropathy and myopathy	Variable	Denervation atrophy and myopathy	Variable

From Bolton CF, Young GB: Neurological complications in critically ill patients. p. 981–997. In Aminoff MJ (ed) Neurology and General Medicine. 4th Ed. Churchill Livingstone Elsevier, Philadelphia, 2008, with permission.

establishing a neuromuscular basis for respiratory impairment in critically ill patients. These diagnostic modalities may also indirectly implicate impairment of "central drive" when the deficit is in the CNS centers of respiration. This electrodiagnostic testing complements other indicators of respiratory function including vital capacity and maximum inspiratory and expiratory pressures; it may help with the decision for intubation and ventilatory support.

Disorders of Nerve

CRITICAL ILLNESS POLYNEUROPATHY

Critical illness polyneuropathy (CIP) was first described in the 1980s by Bolton, Zochodne, and colleagues, and the diagnostic criteria currently employed are shown in Table 56-3. It is the most frequent acute polyneuropathy seen in critical care, and it may affect half to three-quarters of ICU patients to some degree.[9] Patients may exhibit both limb and respiratory muscle weakness; failure to wean from mechanical ventilation is a common presenting feature and may be the only identified sign of the condition. This cause of failure to wean is important to differentiate from other potential etiologies including encephalopathy-related central drive failure, phrenic nerve trauma, neuromuscular junction dysfunction, and myopathy. Decreased maximal inspiratory and expiratory pressures and vital capacities usually correlate with limb muscle weakness and are associated with delayed extubation, prolonged ventilation, and unplanned readmission to the ICU.

Facial muscles are typically spared in CIP. This feature allows for the recognition of a fairly specific pattern of preserved facial grimacing with flaccid or absent limb movements in response to centrally/axially located noxious stimuli such as sternal rub or supraorbital ridge pressure (the usual length-dependent axon loss pattern may make deep nailbed pressure a less reliable noxious stimulus option). Typically there is loss of

TABLE 56-3 ■ Diagnostic Criteria for Critical Illness Polyneuropathy

1. The patient is critically ill (multiorgan dysfunction and failures)
2. Limb weakness or difficulty weaning patient from ventilator after non-neuromuscular causes such as heart and lung disease have been excluded
3. Electrophysiologic evidence of axonal motor and sensory polyneuropathy
4. Absence of a decremental response on repetitive nerve stimulation

Definite diagnosis of critical illness polyneuropathy is established if all four criteria are fulfilled. Probable diagnosis of critical illness polyneuropathy is established if criteria 1, 3, and 4 are fulfilled. Diagnosis of intensive care unit—acquired weakness is established if only criteria 1 and 2 are fulfilled.

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deep tendon reflexes which were previously demonstrable. In the uncommon circumstance where the patient is sufficiently alert, muscle strength can be tested using the Medical Research Council (MRC) scale or handgrip dynamometry. An "MRC sum score" of less than 48 establishes ICU-acquired paresis and is associated with protracted mechanical ventilation and length of stay in the ICU, increased mortality, and reduced quality of life in survivors.[10,11] Although predominantly motor deficits are manifest, loss of pain, temperature, joint position, and vibration sensation may also be noted. In some instances, weakness may appear to be more generalized rather than clearly length-dependent. Although most patients improve, the degree of residual disability after discharge from the acute care setting is variable and correlates robustly with the severity of electrodiagnostic findings.

Laboratory findings may be consistent with SIRS, sepsis, multiorgan failure, or a combination of the three. Lumbar puncture is not usually required but will typically show a normal CSF protein concentration and no albuminocytologic dissociation as would be seen with Guillain—Barré syndrome.

The pattern of electrodiagnostic abnormalities seen in CIP is typically consistent with a length-dependent, sensorimotor, axonal polyneuropathy. Hence, the initial changes are marked by a reduction in the amplitude of sensory nerve action potentials (SNAPs) and compound muscle action potentials (CMAPs), predominantly in the lower extremities. In keeping with this axon-loss picture, demyelinating features including prolongation in distal latencies, slowing of conduction velocities, temporal dispersion of CMAPs, and conduction block are either absent or minimal (Fig. 56-2).

It may not be possible to elicit motor unit potentials on needle electrode examination if consciousness is markedly depressed. It typically takes 2 to 3 weeks after

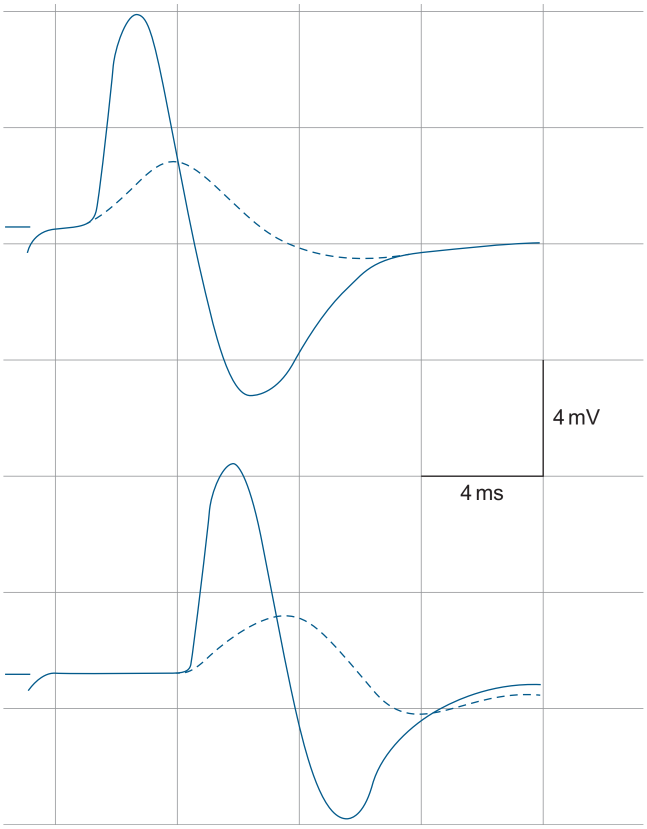

FIGURE 56-2 ■ Compound muscle action potential recording from the thenar muscle on stimulation of the median nerve at the wrist and elbow, at the onset of sepsis (*A, solid line*) and 3 weeks later (*B, dotted line*). Note the marked drop in amplitude and mild but definite increase in duration without a change in latency. (Reprinted with permission from Latronico N, Bolton CF: Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol 10:931, 2011, modified from Bolton CF, Young BG, Zochodne DW: Neurological changes during severe sepsis. p. 180. In Dobb GJ, Burehardi H, Dellinger RP (eds): Current Topics in Intensive Care, Saunders, London, 1994.)

initial nerve injury for the emergence of abnormal spontaneous activity including positive sharp waves and fibrillation potentials. By this time, there is further reduction of the SNAPs and CMAPs due to ongoing axon loss.

As recovery occurs in CIP, spontaneous activity tends to subside. By about 2 months, motor unit potential morphology changes will include increased amplitude and duration along with the presence of polyphasia. Patients at risk for CIP may benefit from having serial fibular (peroneal) motor nerve conduction studies.

The specific clinical and electrodiagnostic features of CIP usually obviate the need for tissue diagnosis. However, distal-predominant motor and sensory nerve fiber degeneration have been demonstrated on nerve and muscle biopsies as well at autopsy in patients with CIP (Figs. 56-3 and 56-4). Histopathologic examination reveals acute denervation atrophy of muscle, including both type I and type II fibers, with scattered, angulated fibers (Fig. 56-5). As the process advances, there is some degree of reinnervation, and therefore fiber-type grouping. Inflammation in either nerve or muscle is conspicuously absent. The CNS is generally devoid of changes except for chromatolysis of the anterior horn cells secondary to distal motor axonal injury. Intercostal and phrenic nerves undergo a similar process of motor axon loss, resulting in denervation atrophy of respiratory muscles, which explains the associated respiratory compromise.

The major risk factors for CIP include SIRS, sepsis, multiorgan failure, and hyperglycemia. Associations with corticosteroids are often cited but have not been definitively proven.

More recent research has demonstrated a component of potentially reversible functional disruption

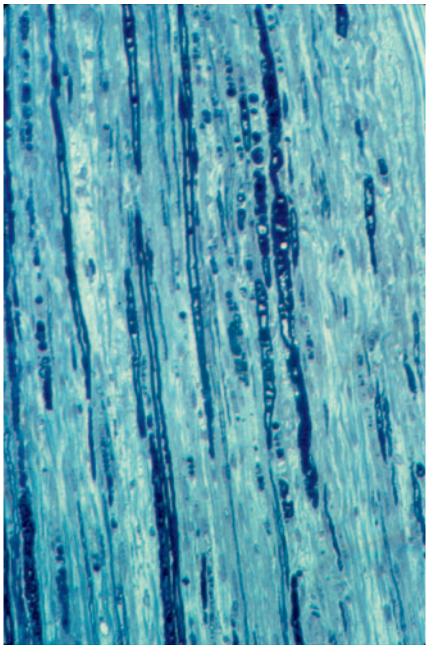

FIGURE 56-4 ■ Longitudinal section of the deep fibular (peroneal) nerve demonstrating axonal degeneration and loss of myelinated fibers. (Toluidine blue; original magnification 778 ×.) (From Zochodne DW, Bolton CF, Wells GA, et al: Critical illness polyneuropathy: a complication of sepsis and multiple organ failure. Brain 110:819, 1987, with permission.)

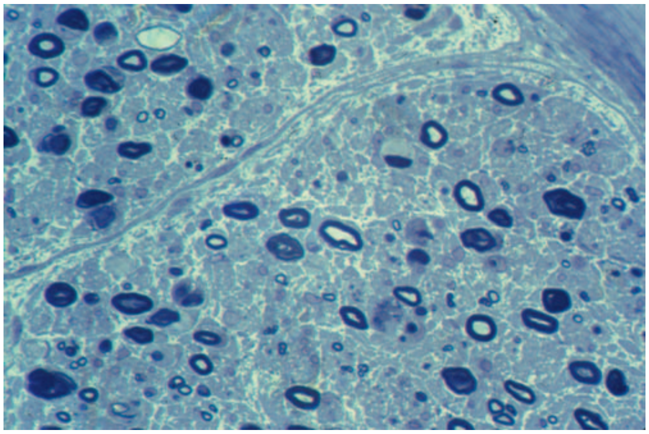

FIGURE 56-3 ■ Transverse section of the superficial fibular (peroneal) nerve showing severe axonal degeneration and loss of myelinated fibers. (Toluidine blue; original magnification 773 ×.) (From Zochodne DW, Bolton CF, Wells GA, et al: Critical illness polyneuropathy: a complication of sepsis and multiple organ failure. Brain 110:819, 1987, with permission.)

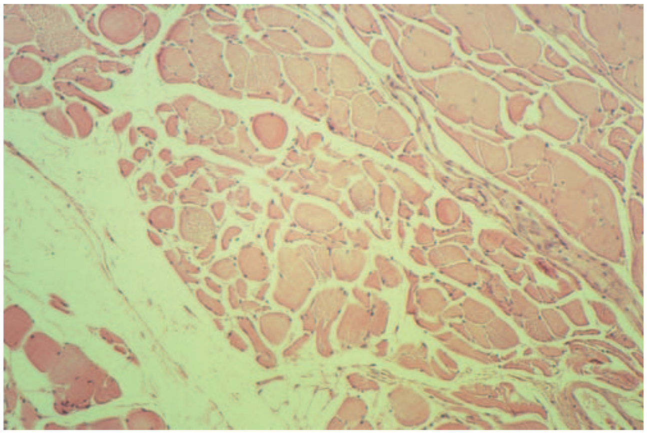

FIGURE 56-5 ■ Transverse section of iliopsoas muscle showing scattered and grouped atrophic fibers consistent with denervation atrophy. (Hematoxylin and eosin; original magnification 195 ×.) (From Zochodne DW, Bolton CF, Wells GA, et al: Critical illness polyneuropathy: a complication of sepsis and multiple organ failure. Brain 110:819, 1987, with permission.)

that precedes structural degeneration of nerves in CIP. Such a phenomenon is mirrored simultaneously in multiple failing organs and is likely a result of shared microcirculatory, cellular, and metabolic pathophysiologic mechanisms. This may be the basis for electrophysiologic changes in peripheral nerves, which have rapid onset and may be reversible. Correspondingly, onset of clinical signs can also be rapid and reversible. Data have suggested that the physiologic basis of this reversible peripheral nerve dysfunction may lie in abnormal nerve excitability due to an induced channelopathy, namely a shift in the voltage dependence of sodium channel fast inactivation toward a more negative potential.

Apart from mitigating systemic and microcirculatory factors that promote peripheral nerve ischemia, there is evidence for mitochondrial dysfunction with reduced ATP biosynthesis and energy generation (cytopathic hypoxia).[9] Metabolic disruptions include an increase in the production of cytokines, nitric oxide, and stress hormones which can lead to hyperglycemia from increased insulin resistance. Decreased metabolic demands reduce hormonal stimulation which, in conjunction with direct mitochondrial inhibition from nitrogen and oxygen reactive species, leads to mitochondrial ATP generation failure.[9] Consequently, impairment in the axonal transport systems due to energy failure may be responsible for distal-predominant nerve fiber involvement.

In patients with CIP, the vascular endothelium of epineurial and endoneurial vessels demonstrates increased expression of E-selectin, a marker of endothelial cell activation. As a consequence, activated leukocytes within the endoneurial space produce local cytokines, which increase microvascular permeability. The subsequent endoneurial edema compromises the blood–nerve barrier. Such deleterious fluid dynamics are enhanced by hyperglycemia and hypoalbuminemia. The peripheral nerve axon which is "exposed" to this process is therefore further susceptible to circulating toxins in the setting of sepsis.

Recommendations for patient management will necessarily include the prevention and aggressive treatment of sepsis and related multiple organ failure. Although malnutrition is not clearly implicated in the pathogenesis of CIP, benefits are predictable if nutritional status is optimized with the timely use of total parenteral or enteral nutrition. Early intervention with rehabilitative exercises should be encouraged.

In the treatment of CIP, there is no definite evidence to support the use of intravenous immunoglobulin or other agents (e.g., antioxidants, hormones) thought to abort the septic cascade. Intensive insulin therapy to maintain euglycemia reduces the incidence of CIP and the duration of mechanical ventilation in both surgical and medical critically ill patients. Studies have demonstrated a 20 to 44 percent reduction in the incidence of neuromuscular dysfunction in patients receiving intensive treatment for hyperglycemia.[9] However, the optimum glycemic target is undetermined because intensive insulin therapy required to maintain strict blood glucose control also increases mortality in adult ICU patients.

The underlying condition is responsible for a mortality rate of up to 50 percent in patients with CIP. About one-fifth of patients with CIP have severe residual deficits one year after acute illness.

MOTOR NEUROPATHY AND NEUROMUSCULAR BLOCKING AGENTS

Competitive (nondepolarizing) neuromuscular blocking agents including pancuronium and vecuronium have been associated with electrophysiologic evidence of long-term neuromuscular junction dysfunction and polyneuropathy. These agents have been traditionally used for muscular relaxation during mechanical ventilation. Discontinuation after prolonged use is associated with difficulty in weaning the patient from the ventilator. In these cases, limb weakness is also common. Under these circumstances, injury appears to occur at multiple sites. A myopathic component is suggested by a mild-to-moderate elevation in the serum creatine kinase (CK). Impairment of postsynaptic neuromuscular junction transmission can be found on low-frequency repetitive nerve stimulation testing. Motor-predominant axonal loss is detected on nerve conduction studies.

It is unclear whether denervation occurs as a primary or secondary process. In some circumstances there may be no actual axonal disruption. Electrodiagnostic findings may thus be the result of profound and prolonged neuromuscular junction blocking. This phenomenon is thought to produce a "functional denervation" in affected muscles, which may manifest varying degrees of denervation atrophy and muscle necrosis.

There has been speculation about a major role of sepsis in the pathogenesis of this condition. Proponents of this believe that if the various systemic complications of sepsis can be treated successfully, spontaneous improvement and rapid recovery may ensue. It is generally recommended that dose and duration of neuromuscular blocking agents be judiciously minimized as a reasonable preventive measure.

Fortunately, the routine use of pancuronium and vecuronium for ventilated, critically ill patients is less common. When neuromuscular blockade is required, the use of alternative nondepolarizing agents is recommended. It appears that cisatracurium besylate improves survival and decreases mechanical ventilation time in patients with the acute respiratory distress syndrome, with no significant deleterious effects on muscle function.

Chronic Polyneuropathies

On occasion, the neuropathy found in the critically ill patient may represent an exacerbation or worsening of previous deficits associated with a longstanding chronic polyneuropathy. This neurologic decompensation may manifest itself as sensorimotor deficits in the limbs as well as respiratory muscle weakness. Patients who may be affected in this manner include those with chronic inflammatory demyelinating polyneuropathy and even patients with significant diabetic polyneuropathy.

These cases are best confirmed with electrodiagnostic studies. Apart from conventional limb EMG, phrenic nerve conduction study and diaphragmatic needle electrode examination (possibly with neuromuscular ultrasound) are often helpful.

Neuromuscular Junction Transmission Disorders and Myopathies

Features of pre-existing neuromuscular junction transmission disorders and myopathies are difficult to differentiate from the myriad of possible causes of muscular weakness in the critical care setting. A fatigable pattern of weakness with prominent oculobulbar findings should raise suspicion for a neuromuscular junction disorder. It is not unusual for myopathies to transiently worsen with intercurrent illness as well. One should be particularly mindful of the patient with central core disease in whom malignant hyperthermia is a significant risk. Succinylcholine and volatile anesthetics should be strictly avoided. Electrodiagnostic studies with repetitive nerve stimulation and (infrequently) muscle biopsy may be employed to establish the specific diagnosis and differentiate from the more common etiologies in the ICU.

Transient Neuromuscular Junction Blockade

In cases where neuromuscular junction blocking agents are used for muscle relaxation in mechanically ventilated patients, normal liver and kidney function facilitates rapid metabolism and clearance of the drug. However, in critical illness, renal and hepatic function may be compromised. Consequently, it has been postulated that neuromuscular junction blocking agents may remain active long after discontinuation due to the protracted half-life in these patients. This feature may augment some of the neuromuscular junction injuries attributed to sepsis itself, and convalescence may require weeks to months. Electrodiagnostic evaluation with repetitive nerve stimulation may help in the confirmation and quantification of this deficit.

Critical Illness Myopathy

While CIP was being better characterized in the 1980s, clinicians were also appreciating an acute myopathy in severely ill patients treated for conditions like status asthmaticus and organ transplantation. Various terms have marked the condition's etymologic evolution including acute quadriplegic myopathy, critical care myopathy, acute necrotizing myopathy of intensive care, thick filament myopathy, pancuronium-associated myopathy, and acute corticosteroid myopathy. Eventually, the name critical illness myopathy was accepted for standard reference.

Although critical illness myopathy may occur independently of CIP, the conditions most often co-exist. Difficulty with differentiation has led to the nonspecific but frequent reference to "polyneuromyopathy" in the literature. Data have shown a strong correlation between severity of critical illness including sepsis and the early onset and severity of CIP and myopathy. Patients at particular risk for critical illness myopathy include those with status asthmaticus, among whom up to one-third may be affected. It may also be seen in about 7 percent of patients after orthotopic liver and heart transplantation.[9] A predisposition for myopathy in transplant populations with renal failure has been demonstrated. Data also support corticosteroids and neuromuscular junction blockers as risk factors, especially when biopsy shows myosin loss.

Although this is an acute illness, the exact time of onset is often difficult to decipher in the context of a septic encephalopathy and administration of centrally acting sedative medications and neuromuscular blocking agents. The most prominent clinical feature is that of generalized flaccid weakness affecting appendicular, truncal, and cranial musculature. There is usually no myalgia or muscle tenderness. An important manifestation is neck flexor weakness, which correlates with diaphragmatic muscular weakness and difficulty in weaning from mechanical ventilation. Although a pupil-sparing ophthalmoparesis may be present, this feature often prompts further exclusion of a neuromuscular junction transmission disorder. The loss of deep tendon reflexes is a variable finding, although in most cases they are depressed.

In the laboratory evaluation of these patients, serum CK levels are usually mildly increased with studies showing elevation in at least 50 percent. This is in contrast to patients with CIP who typically have normal to minimally elevated serum CK levels. A patient receiving corticosteroids may have at least a 10-day delay in CK elevation related to critical illness myopathy. Most striking elevations of serum CK are seen with necrotizing myopathies and rhabdomyolysis where there is often concomitant myoglobinuria.

In critical illness myopathy, typical findings on nerve conduction studies are low-amplitude CMAPs, which are often two to three times longer in duration than in healthy individuals and are most pronounced in the lower limbs. Slowing of muscle fiber conduction has been one proposed explanation. SNAPs are expected to be normal but may be technically difficult to obtain due to skin conditions and tissue edema.

The needle electrode examination often shows evidence of spontaneous activity including fibrillation potentials and positive sharp waves, which are thought to reflect muscle fiber membrane disruption. Activation typically reveals "myopathic" motor unit potentials with short duration and low amplitudes; there is an increased number of polyphasic potentials and normal or early recruitment, with high-frequency components. In unresponsive patients, some authors have suggested utility of recordings from the tibialis anterior, employing reflexive activation after plantar stimulation. Alternatively, direct muscle stimulation may be used; although this is a technically challenging test with limited availability, it can demonstrate reduced muscle membrane excitability, established if the CMAP amplitude after direct muscle stimulation is less than 3 mV and the ratio of the CMAP amplitude after nerve stimulation to that obtained after direct muscle stimulation is more than 0.5. Additionally, since a response to direct muscle stimulation but not corresponding nerve stimulation is seen in CIP, this electrodiagnostic test may be helpful in differentiating between these two related conditions. It is less helpful when both disorders co-exist. For a diagnosis of "definite" critical illness myopathy, repetitive nerve stimulation testing should be done to demonstrate the absence of a decremental response seen in neuromuscular junction transmission disorders such as myasthenia gravis. Other criteria are shown in Table 56-4.

In the critically ill myopathic patient with respiratory impairment, findings on phrenic nerve conduction studies and needle electrode examination of the diaphragm may be similar to those in CIP. Motor unit potentials occurring during attempted inspiration or sniffing tend to have a myopathic appearance, thus posing difficulty in distinguishing neuropathy from myopathy.

Being able to recognize the described pattern of clinical features, laboratory abnormalities, and electrodiagnostic findings should minimize cases requiring biopsy for diagnosis. A biopsy is helpful in cases where another myopathic process needs to be excluded or where a tissue diagnosis will change management. Typical muscle biopsy findings

TABLE 56-4 ■ Diagnostic Criteria for Critical Illness Myopathy

1. The patient is critically ill (multiorgan dysfunction and failures)
2. Limb weakness or difficulty weaning patient from ventilator after non-neuromuscular causes such as heart and lung disease have been excluded
3. CMAP amplitudes less than 80% of the lower limit of normal in two or more nerves without conduction block
4. Sensory nerve action potential amplitudes more than 80% of the lower limit of normal
5. Needle electromyography with short-duration, low-amplitude motor unit potentials with early or normal full recruitment, with or without fibrillation potentials in conscious and collaborative patients; or increased CMAP duration or reduced muscle membrane excitability on direct muscle stimulation in noncollaborative patients
6. Absence of a decremental response on repetitive nerve stimulation
7. Muscle histopathologic findings of primary myopathy (e.g., myosin loss or muscle necrosis)

Definite diagnosis of critical illness myopathy is established if all seven criteria are fulfilled. Probable diagnosis of critical illness myopathy is established if criteria 1 and 3–6 are fulfilled. Diagnosis of intensive care unit-acquired weakness is established if only criteria 1 and 2 are fulfilled. CMAP, compound muscle action potential.

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in this condition include type II—predominant fiber atrophy with myofibrillar disorganization. There may be variable degrees of both necrosis and myofiber regeneration. Thick-filament myosin loss is the most characteristic feature and may be related to a decreased transcription rate or loss of myosin messenger RNA.

The underlying pathophysiology of critical illness myopathy is still being elucidated. Studies have demonstrated electrical inexcitability of muscle due to a shift in the voltage dependence of sodium channel fast inactivation similar to that seen in CIP. This process seems to be augmented by sepsis. Evidence also supports muscle perfusion deficits at the capillary level. Muscle wasting is primarily due to degradation of myofibrillar proteins, which comprise 60 to 70 percent of total muscle protein. As a consequence, there is prominent loss of myosin filaments with sarcomeric disorganization. Similar to what is seen in CIP and other organ failure during sepsis, there is muscle fiber bioenergetic failure due to mitochondrial dysfunction. Toxicity appears to be mediated by ATP depletion, intracellular antioxidant diminution, and nitric oxide production.

A paradigm shift is occurring in the rehabilitation management of patients with critical illness myopathy. New evidence supports earlier initiation of rehabilitative exercises without the previous delay until the patient was deemed clinically stable or "medically optimized." Serial muscle biopsies have shown that repeated daily passive mobilization prevents muscle atrophy. Although muscle strength is not greatly improved, early physical and occupational therapy while in the ICU improves functional independence, decreases delirium, and increases the number of ventilator-free days compared to standard care. Although the application has been relatively limited thus far, the use of a bedside ergometer for daily cycle sessions as early as possible after ICU admission improves functional exercise capacity, quadriceps muscle force, and perceived functional status.[12]

Consistent with current practice trends, paralytic agents in the mechanically ventilated patient should be limited. Furthermore, the duration of mechanical ventilation, coma, and the overall ICU and hospital stay may be reduced with a protocol of coordinated daily interruption of sedatives and interruption of mechanical ventilation with spontaneous breathing trials. With these "sedation vacation exercises," there is also improvement in 1-year survival.

THICK-FILAMENT MYOSIN LOSS

This feature has been specifically associated with the term "acute quadriplegic myopathy" and is also referred to as "myosin-deficient" myopathy. Classically, cases are seen in severe asthmatic and post-transplant patients who are intubated and mechanically ventilated after receiving high-dose corticosteroids and neuromuscular blocking agents. There may be a slight elevation in serum CK, and muscle biopsy shows selective loss of thick (myosin) filaments. Although these changes can be seen on light microscopy, they are better appreciated on electron microscopy where varying degrees of necrosis can also be seen (Fig. 56-6).

In the absence of any specific treatment, it is recommended that corticosteroids and neuromuscular

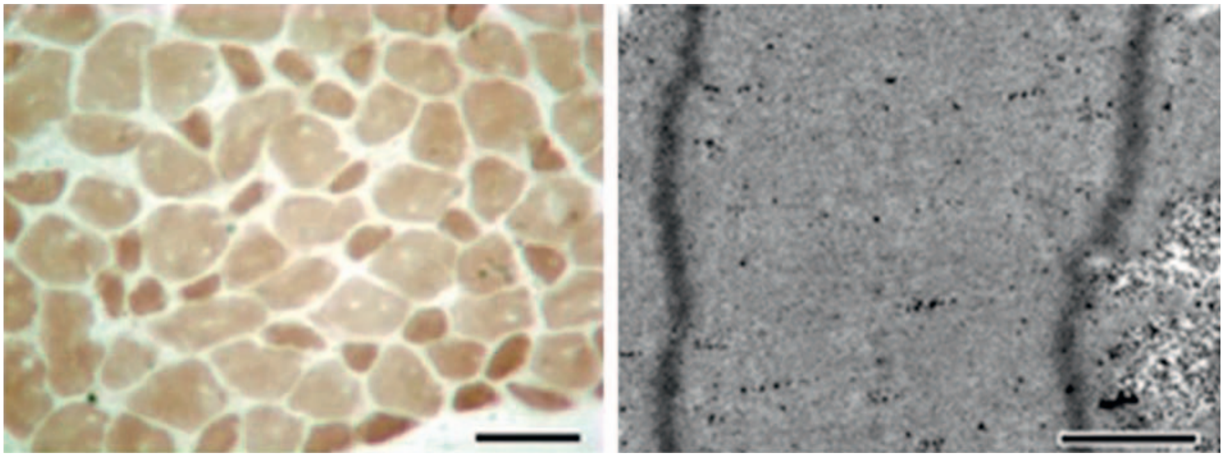

FIGURE 56-6 ■ Critical illness myopathy. (*Left*) ATPase enzyme histochemistry at pH 9.8 shows atrophy of type II (dark) fibers. Scale bar, 100 μm. (*Right*) Electron micrograph demonstrating loss of thick filaments. Scale bar, 0.5 μm. (Courtesy Susan M. Staugaitis, M.D., Ph.D., Cleveland Clinic.)

blocking agents be avoided or limited as much as possible. With recovery, there is a gradual reduction in myonecrosis and reappearance of thick myosin filaments.

RHABDOMYOLYSIS

Rhabdomyolysis is another muscle complication that can occur in the context of critical illness with corticosteroid and neuromuscular blocking agent use. It may result from many causes, presenting with myalgia, muscle tenderness, weakness, and possible swelling. It is associated with hyperkalemia and hypocalcemia, placing the patient at risk for cardiac arrhythmias. There is also a significant risk for acute renal failure, especially from marked myoglobinuria. Extensive myolysis results in serum CK levels that are frequently above 10,000 IU/L.

The electrodiagnostic findings are consistent with an acute myopathy, with motor and sensory nerve conduction studies typically being normal. The needle electrode examination usually reveals normal motor unit morphology with scant fibrillation potentials. A muscle biopsy is usually not required, but the tissue may show a variable degree of myonecrosis without inflammation or any other specific pathologic features. Rarely in bacteremic patients, muscle biopsy may confirm microabscesses (mostly seen in tropical countries or in children). With appropriate supportive therapy and treatment of the underlying condition, patients with rhabdomyolysis usually have a good functional prognosis.

ACUTE NECROTIZING MYOPATHY OF INTENSIVE CARE

This condition is considered a more “malignant” variant of rhabdomyolysis. In this subtype, there is no particular etiologic difference; however, serum CK levels are greatly elevated and there is florid myoglobinuria. Biopsy demonstrates extensively severe myonecrosis. In severe cases, the prognosis is particularly poor as significant muscle weakness may persist.

CACHECTIC MYOPATHY

This entity constitutes the weakness and atrophy related to extensive disuse or catabolic predisposition in patients with starvation and malnutrition. Patients at particular risk include those with anorexia nervosa or those following gastric bypass surgery. Cachectic myopathy is not uncommon in the ICU. The condition is characterized by normal serum CK levels and electrodiagnostic findings. The only abnormality on muscle biopsy may be type II fiber atrophy. The prognosis is quite variable and is related to the underlying disease.

Co-existing Critical Illness Polyneuropathy and Myopathy

As may be expected, the precise incidence of CIP and critical illness myopathy is difficult to ascertain because of wide variability in the study population, overlapping features, risk factors, the timing of assessment, and the diagnostic criteria used. It has been reported that in patients mechanically ventilated for 4 to 7 days or with increased risk of developing multiorgan failure, the incidence was 25 to 33 percent on clinical assessment and 30 to 58 percent with electrodiagnostic assessment.[10,11,13,14] Prospective studies have identified independent risk factors which include severity of illness, multiple (≥2) organ dysfunction, duration of vasopressor support, duration of ICU stay, hyperglycemia, female sex, renal failure and renal replacement therapy, hyperosmolality, parenteral nutrition, low serum albumin, and neurologic failure. Furthermore, aminoglycoside antibiotics, neuromuscular junction blocking agents, and corticosteroids have been implicated as risk factors in some studies.[9]

There is significant logistical difficulty in separating CIP from critical illness myopathy. Critical illness myopathy is often more challenging to diagnose since it may require more technical electrodiagnostic modalities, more sophisticated expertise, and ultimate confirmation with muscle biopsy. There is evidence to suggest that once these diagnostic methodologies are employed, critical illness myopathy is more predominant where previously mixed etiologies were diagnosed.

Nonetheless, most cases of neuromuscular weakness in the ICU may have a component of both CIP and myopathy. Accordingly, there may be overlapping clinical, laboratory, electrodiagnostic, and biopsy findings.

There is evidence that indicates that both CIP and critical illness myopathy cause limb and diaphragm weakness that persists for months or years after resolution of critical illness. Nearly one-third of patients with either or both of these conditions do not recover independent ambulation or spontaneous ventilation. CIP has been identified as the main contributor to persistent disability while critical illness myopathy is more frequently associated with complete recovery. Patients with either or both conditions are likely to benefit from fastidious treatment of infection, optimized nutrition, correction of underlying metabolic and electrolyte disturbances, deep vein thrombosis prophylaxis, chest physiotherapy and pulmonary toilet, frequent turning and pressure point padding, orthotics use, and a proactive physical therapy regimen.[15]

CONCLUDING COMMENTS

The complications of systemic inflammation in the context of critical illness affect both the central and peripheral nervous systems through a variety of mechanisms that allow inflammatory mediators among other culprits to gain access though the blood–brain or blood–nerve barrier. Optimal treatment involves early recognition and treatment of the underlying illness, with optimization of glycemic control and judicious use of corticosteroids and neuromuscular junction-blocking agents. Early mobilization and rehabilitation are proven to improve recovery time and functional independence. Electrodiagnostic tests are helpful for both diagnosis and prognostication.

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CHAPTER

57

Seizures and General Medical Disorders

SIMON M. GLYNN ■ JACK M. PARENT

RENAL FAILURE
  Use of Antiseizure Medications in Renal Disease
HEPATIC DISEASE
  Antiseizure Medications and Hepatic Injury
CARDIAC DISEASE
  Use of Antiseizure Medications in Cardiac Disease
SEIZURES IN CRITICALLY ILL PATIENTS
  Nonconvulsive Seizures and Status Epilepticus
  Treatment of Seizures in Critically Ill Patients
  Seizures Caused by Anoxic-Ischemic Encephalopathy
INFLAMMATORY AND AUTOIMMUNE DISEASES AND EPILEPSY
  Limbic Encephalitis
  Connective Tissue Diseases and Cerebral Vasculitis
  Thyroid Disease and Hashimoto Encephalopathy
  Inflammatory Bowel Disease
  Diabetes and GAD65 Antibodies
  Multiple Sclerosis and Other Demyelinating Diseases
HEPATIC PORPHYRIAS
SEIZURES IN TRANSPLANT RECIPIENTS
HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND SEIZURES
SEIZURES ASSOCIATED WITH SYSTEMIC CANCER
ENDOCRINE OR METABOLIC DISORDERS
  Disorders of Glucose Metabolism
  Thyroid Disease
  Disorders of Sodium Homeostasis
  Calcium and Magnesium Imbalance
SEIZURES RELATED TO ALCOHOL, MEDICATIONS, AND RECREATIONAL DRUGS
  Alcohol
  Cocaine and Other Recreational Drugs
  Medications
    Antidepressant Drugs
    Antipsychotics and Lithium
    Antibiotics
    Other Medications That May Cause Seizures
CEREBRAL TRAUMA, SEIZURES, AND EPILEPSY

Seizures commonly arise in persons without epilepsy as a symptom of various general medical disorders, and they can have important implications for the treatment and prognosis of the primary disease. The occurrence and management of seizures in common medical conditions are discussed in this chapter. Attention is also directed at certain less common medical diseases in which seizures are a relatively frequent complication, and at the treatment of pre-existing epilepsy in patients with medical conditions that might complicate management. Selected therapeutic agents and recreational drugs that may cause seizures are reviewed.

Several basic points deserve emphasis. First, in persons with pre-existing epilepsy, seizures frequently worsen during an acute medical illness that typically would not result in seizures. Their occurrence may relate to a lowering of the seizure threshold by metabolic derangements, fever, impaired sleep, or other factors. Antiseizure medications (ASMs) may have to be increased, and benzodiazepines frequently are given also to prevent seizures during the acute illness. These medication changes are usually temporary and do not need to be continued.

Second, seizures provoked in persons without pre-existing epilepsy by an acute metabolic derangement or brain insult are relatively common. Such seizures do not in themselves necessitate a diagnosis of epilepsy and are termed *acute symptomatic seizures* (previously termed provoked seizures or situation-related seizures). In these patients, recognizing and treating the underlying medical illness early is imperative. Acute symptomatic seizures may occur with disorders that are transient and reversible (e.g., alcohol intoxication) or in the acute phase of an irreversible brain injury (e.g., stroke)

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that may subsequently lead to the development of spontaneous recurrent seizures (epilepsy). Although persons experiencing acute symptomatic seizures from a brain insult may be at an increased risk for developing epilepsy in the future, this risk is clearly less than for unprovoked seizures and probably is explained by different neurophysiologic mechanisms. As a corollary, most persons with acute symptomatic seizures are started on ASMs during the acute illness, but do not require long-term ASM treatment.[1]

Finally, acute symptomatic seizures in comatose or critically ill patients can be difficult to recognize, as seizures in these patients may have only subtle or no clinical manifestations. Electroencephalography (EEG) is required in such circumstances to evaluate for seizures and to guide therapies, as discussed in a later section.

RENAL FAILURE

Seizures are common in acute uremia, typically developing between 7 and 10 days after the onset of renal failure, while the patient is anuric or oliguric. By contrast, seizures are relatively unusual in chronic renal insufficiency, and usually only occur if a significant encephalopathy is present. Risk factors for acute symptomatic seizures in renal failure include metabolic disturbances, especially hypocalcemia and hypomagnesemia, which may increase the risk for convulsive status epilepticus, and impaired renal clearance of proconvulsant medications (e.g., penicillin).

Hypertensive encephalopathy is a classic disorder associated with renal failure and blood pressure fluctuations (with the level usually exceeding 180/120 mmHg) that presents with altered mental status and headache. Generalized convulsive seizures are seen in most patients and may be the presenting symptom. Treatment is with intravenous antihypertensive medications to reduce blood pressure by 25 percent within the first hour and then to less than 160/110 mmHg by 6 hours.[2]

Hemodialysis also increases the risk for generalized convulsive seizures, usually toward the end of a hemodialysis session and for several hours thereafter, as part of the *dialysis disequilibrium syndrome.* Fluid shifts may be responsible, leading to cerebral edema from increased brain osmolality in the uremic state. Improved dialysis techniques have reduced the incidence of seizures. The dialysis encephalopathy (dementia) syndrome of myoclonus, asterixis, a distinctive speech disorder, psychiatric disturbances, and seizures due to increased aluminum levels in the brain has largely disappeared in clinical practice in response to removing aluminum from the dialysate.

Prominent myoclonus as well as asterixis (in which the hands flap due to momentary "negative" myoclonus) is often seen in renal failure. Usually, myoclonus occurs in the context of encephalopathy, and may or may not be epileptic. Cephalosporins, amlodipine, verapamil, diltiazem, and nifedipine may induce acute myoclonic jerking without convulsive seizures. Metformin in the presence of end-stage renal disease and pregabalin (frequently prescribed for diabetic neuropathic pain) may also induce myoclonus in patients receiving hemodialysis.

Use of Antiseizure Medications in Renal Disease

The treatment of seizures in renal failure requires both the correction of metabolic abnormalities and the use of ASMs. Several points regarding ASMs in renal impairment are important to remember. First, newer third- and fourth-generation ASMs tend to be cleared renally and should be used cautiously in patients with renal impairment or failure. If used, these newer ASMs usually require dose adjustments in the setting of reduced renal function. Conversely, earlier first- and second-generation ASMs do not usually require dose adjustments for renal function. However, uremic molecules may downregulate the expression of cytochrome P-450 enzymes, thereby decreasing hepatic metabolism and increasing the risks of drug toxicities for these earlier first- and second-generation ASMs that are hepatically metabolized (Table 57-1).

Second, many ASMs bind extensively to serum albumin (Table 57-1). Patients with chronic renal disease are hypoalbuminemic, so protein binding is decreased; a larger amount of free drug is therefore available to exert a pharmacologic effect. Uremic molecules may also bind to plasma proteins, displacing drugs. For these reasons, the free serum level—where available—should guide therapy.

Third, some ASMs are cleared by dialysis. As molecular size decreases, solubility increases such that the fraction removed increases. Conversely, as protein binding increases and the volume of distribution decreases, the fraction removed declines. Highly lipophilic ASMs with large volume and tissue distribution are less available for removal by dialysis. This volume is independent of renal clearance, and usually is not modified in renal impairment (Table 57-1). For this reason, ASMs that are cleared significantly by hemodialysis should be taken after the dialysis session or supplemental doses should be prescribed.

TABLE 57-1 ■ Selected Pharmacokinetics of Antiseizure Medications

		Volume of Distribution (V_d L/kg) (0.6 = V_d for H_2O)	Renal Elimination	Hepatic Metabolism	Molecular Weight (Hemodialysis More Effective if Low)
First- and Second-Generation ASMs					
Minimal or no protein binding	Ethosuximide[*]	0.6–0.7	Minimal	High	141
	Primidone	0.4–1.0	Minimal	High	218
Moderate protein binding	Phenobarbital	0.5–1.0	Minimal	High	232
High protein binding	Benzodiazepines, including Clobazam	1.4–1.8(CLZ), 1.1–3.4(DZP), 1.3(LZP)	Minimal	High	300(CLZ), 284(DZP), 321(LZP)
	Carbamazepine	0.8–2.0	Minimal	High	236
	Phenytoin	0.5–1.0	Minimal	High	252
	Valproic acid	0.14–0.23	Minimal	High	144
Third- and Fourth-Generation ASMs					
Minimal or no protein binding	Eslicarbazepine	–	Minimal	High	296
	Felbamate	0.7–1.0	Moderate	Moderate	238
	Gabapentin[*]	0.8–1.8	High	None	171
	Lacosamide	0.6	Minimal	Moderate	250
	Levetiracetam[*]	0.7	Moderate	None	170
	Pregabalin[*]	0.5	High	Minimal	159
	Rufinamide	0.7	Minimal	High	238
	Topiramate	0.6–0.8	Moderate	Moderate	339
	Vigabatrin[*]	1.1	High	None	129
Moderate protein binding	Lamotrigine	0.9–1.3	Minimal	High	256
	Oxcarbazepine[†]	0.7	Minimal	High	252
	Zonisamide	0.8–1.6	Minimal	Moderate	212
	Brivaracetam	0.5	High	High	212
High protein binding	Stiripentol[§]	3.2	Minimal	High	234
	Perampanel[¶]	1.1	Moderate	High	363

ASM, antiseizure medication; CLZ, clobazam; DZP, diazepam; LZP, lorazepam.

[*] Is not protein bound.

[†] The active metabolite 10-OH-carbamazepine is 40% bound (minimal-moderate).

[§] Approved in Europe for SMEI (Dravet syndrome).

[¶] The mean t(1/2) of perampanel is about 105 h, and steady state is achieved in 2–3 weeks; but t(1/2) increases to 305 h in mild hepatic impairment. Dosage adjustments are required in patients with mild or moderate hepatic impairment.

Data from: Israni RK, Kasbekar N, Haynes K, et al: Use of antiepileptic drugs in patients with kidney disease. Semin Dial 19:408, 2006; Diaz A, Deliz B, Benbadis SR: The use of newer antiepileptic drugs in patients with renal failure. Expert Rev Neurother 12:99, 2012; Johannessen Landmark C, Patsalos PN: Drug interactions involving the new second- and third-generation antiepileptic drugs, Expert Rev Neurother 10:119, 2010; and individual product monographs in: Micromedex® Healthcare Series [Internet database]. Thomson Reuters (Healthcare) Inc., Greenwood Village, CO. Updated periodically.

There are few data or systematic reviews on the use of third- and fourth-generation ASMs in renal failure, including patients on dialysis.[3] Data for the pharmacokinetics of individual ASMs and recommended dosing adjustments for newer ASMs are summarized in Tables 57-1 and 57-2, respectively.

HEPATIC DISEASE

Seizures are relatively uncommon in patients with acute hepatic encephalopathy, if seizures related to alcohol withdrawal are excluded. Either focal or generalized seizures may occur, usually in severe hepatic

TABLE 57-2 ■ Dose Adjustments for Selected Newer Antiseizure Medications in Renal Disease

	ASM Dose				
	GFR 60–90 mL/min	**GFR 30–60 mL/min**	**GFR 15–30 mL/min**	**GFR ≤15 mL/min**	**Hemodialysis**
Third- and Fourth-Generation ASMs					
Gabapentin	300–1,200 mg t.i.d	200–700 mg b.i.d	200–700 mg/day	100–300 mg/day	Plus 125–350 mg after HD
Levetiracetam	500–1,000 mg b.i.d	250–750 mg b.i.d	250–500 mg b.i.d	500–1,000 mg/day	Plus 250–500 mg after HD
Topiramate	50% decrease for ≤70 mL/min	50% decrease	50% decrease		Plus 50–100 mg after HD
Zonisamide	100–400 mg/day	100–400 mg/day			
Oxcarbazepine	300–600 mg b.i.d	300–600 mg b.i.d	300 mg/day (starting dose)		
Felbamate	None	50% decrease			
Lamotrigine*	None	None	None	None	
Brivaracetam	None	None	None	None	Not recommended (not studied)
Vigabatrin	25% decrease	50% decrease	75% decrease		
Rufinamide	None	None	None		Plus 30% of dose after HD
Lacosamide	None	None	300 mg/day		Plus ≤50% replacement dose
Perampanel	None	Close monitoring	Not recommended		Not recommended (not studied)
Eslicarbazepine	None	400–600 mg/day	400–600 mg/day		
Clobazam	None	None	None		None
Pregabalin	None	50% decrease	25–150 mg/day	25–75 mg/day	Plus 25–150 mg after HD

*The product monograph for Lamictal XR recommends reduced maintenance doses in patients with significant renal impairment, and caution in patients with severe renal impairment. Lamotrigine pharmacokinetics were essentially unchanged in a study comparing 10 subjects with renal failure (estimated creatine clearance of 10 to 25 mL/min) to 11 healthy subjects (Wootton R, Soul-Lawton J, Rolan PE, et al: Comparison of the pharmacokinetics of lamotrigine in patients with chronic renal failure and healthy volunteers. Br J Clin Pharmacol 43:23, 1997).

Blanks indicate inadequate data, and individual ASMs should be used with caution or avoided in these circumstances. "None" indicates that no change in dose is recommended.

ASM, antiseizure medication; b.i.d, two times daily; t.i.d, three times daily.

Data from: Israni RK, Kasbekar N, Haynes K. et al.: Use of antiepileptic drugs in patients with kidney disease. Semin. Dial. 19:408, 2006; Diaz A, Deliz B, Benbadis SR: The use of newer antiepileptic drugs in patients with renal failure. Expert Rev. Neurother. 12:99, 2012; and individual product monographs in: Micromedex® Healthcare Series [Internet database]. Thomson Reuters (Healthcare) Inc., Greenwood Village, CO. (Updated periodically.)

encephalopathy. Treatment involves management of the hepatic dysfunction and hepatic encephalopathy.

Chronic liver disease does not usually cause convulsions. The occurrence of seizures in alcoholics with hepatic cirrhosis is usually related to alcohol withdrawal. Seizures are common in Reye syndrome and rare in Wilson disease. Convulsions in patients with acute hepatic necrosis are frequently associated with severe hypoglycemia. In these patients, ASM therapy often is not required except when an underlying cause of epilepsy (e.g., prior trauma in an alcoholic) is present.

Antiseizure Medications and Hepatic Injury

Gabapentin, vigabatrin, and levetiracetam are the only ASMs not hepatically metabolized. Certain ASMs, including selected newer agents, undergo extensive hepatic metabolism (Table 57-1), but unless hepatic dysfunction is severe its effects on their pharmacokinetics are difficult to predict. Barbiturates, and benzodiazepines, as well as other central nervous system (CNS) depressants, may unmask hepatic encephalopathy in patients with compensated liver disease, and are relatively contraindicated. Valproic acid is potentially hepatotoxic and should be used with care in patients with pre-existing liver disease. The free fraction of highly protein-bound ASMs may increase due to hypoalbuminemia, and (as for renal impairment) the free serum level—where available—should guide therapy.

In persons without hepatic disease, ASMs may cause drug-induced hepatic injury. In most cases, these reactions are reversible by stopping the ASM but, occasionally, acute hepatic failure may necessitate transplantation. ASMs (as a class) were the third most-common cause (phenytoin, $n = 10$; valproic acid, $n = 10$) of acute drug-induced liver failure requiring liver transplantation in the United States between 1990 and 2002 ($n = 270$).

Overall, the incidence of clinically important hepatotoxicity seems less for third- and fourth-generation ASMs than for older ASMs, but cases of severe hepatotoxicity have been reported for newer ASMs, including lamotrigine, levetiracetam, gabapentin, pregabalin, and oxcarbazepine. Felbamate specifically has been associated with multiple cases of aplastic anemia and acute liver failure, and has a “black box warning” label that restricts its use.

Two types of hepatic injury by ASMs are described. First, ASMs may induce one of several systemic immune-mediated drug hypersensitivity syndromes that may cause hepatic injury and are potentially life-threatening. These syndromes are characterized by fever, rash, and increased serum levels of aminotransferases several weeks after starting an ASM. The risk for these hypersensitivity reactions is highest for first- and second-generation ASMs, and is estimated to be 1 to 10 per 10,000 for phenytoin, carbamazepine, and phenobarbital, but also for lamotrigine (third-generation).[4] For carbamazepine specifically, the *HLA-B* 15:02* allele is strongly associated with Stevens–Johnson syndrome/toxic epidermal necrolysis in Southeast Asia. For this reason, the U.S. Food and Drug Administration (FDA)–approved drug label for carbamazepine now recommends testing for *HLA-B* 15:02* for all patients with ancestry in populations having an increased frequency of *HLA-B* 15:02*, prior to initiating carbamazepine therapy.

Second, first- and second-generation ASMs may cause hepatic injury as a direct effect of hepatic metabolism, and not as a systemic hypersensitivity syndrome. This is a concern specifically for felbamate and (especially in children) valproic acid.[5] For valproic acid, the risk for hepatic injury in young children less than 2 years old and on multiple ASMs is as high as 1 in 800, and the drug is relatively contraindicated in this population. In adults and children, hyperammonemia may be seen with normal liver function tests in the majority of persons on valproic acid, usually with no associated clinical symptoms. Topiramate may increase this risk of hyperammonemic encephalopathy and hepatic injury from valproic acid.

Cannabidiols (CBD) derived from *Cannabis sativa* have become very popular in recent years for a variety of conditions, particularly pain. In June 2018, the first CBD-based drug, Epidiolex, was approved by the FDA for treatment of selected severe epilepsy syndromes (Dravet and Lennox–Gastaut syndromes). In the trials on which approval was based, CBD was associated with elevated serum levels of aminotransferases. Except for Epidiolex, CBD products are not regulated and the risks for hepatic injury are unclear.

CARDIAC DISEASE

Epidemiologic studies have consistently shown that people with epilepsy have a higher prevalence of structural cardiac disease than those without epilepsy, possibly reflecting shared genetic risk factors that affect the heart and brain. Cardiovascular disease also seems to be a significant contributor to the increased mortality of people with epilepsy, compared with the general population. As a group, patients with epilepsy have lower heart rate variability than normal, a finding that predicts arrhythmias and mortality in cardiac patients but is of uncertain significance in epilepsy.

Cardiac disease may also cause epilepsy indirectly due to stroke or from global cerebral ischemia after cardiac arrest. Stroke accounts for about one-third of newly diagnosed seizures in people over the age of 60 years.

The use of first- and second-generation ASMs may also increase cardiovascular disease risks in persons with epilepsy. The enzyme-inducing ASMs phenytoin or carbamazepine may lead to elevated serologic vascular risk markers (e.g., total cholesterol, low-density lipoproteins, homocysteine) and atherosclerosis. Some first- and second-generation ASMs (e.g., valproic acid, carbamazepine) cause weight gain and may increase the risk of developing nonalcoholic fatty liver disease and metabolic syndrome.

Use of Antiseizure Medications in Cardiac Disease

Cardiovascular disease and epilepsy may co-exist, especially in the elderly, persons with congenital cardiac disease, and persons with alcohol and polysubstance use. This complicates treatment of acute seizures and status epilepticus. Intravenous benzodiazepines may cause hypotension in medically ill or elderly patients. Rapid intravenous administration of phenytoin may cause sinus arrest and hypotension; fosphenytoin, a water-soluble prodrug of phenytoin that does not require propylene glycol as a diluent, is generally preferred for treating status epilepticus as its infusion rate is faster and there is a lesser risk of arrhythmia than with phenytoin. In these patient populations, valproic acid, levetiracetam, or lacosamide are preferred if fosphenytoin is not available.

Various cardiac arrhythmias have been described in persons with epilepsy, including ictal asystole (usually self-limiting), postictal asystole (not self-limiting), ventricular tachycardia/ventricular fibrillation, bradycardia, and atrioventricular block. In some epilepsies, these abnormalities may reflect genetic ion channel mutations expressed in the brain as well as in the heart, and may in part explain the increased risk for sudden unexplained death in epilepsy (SUDEP). The most recognized example of this is Dravet syndrome, a severe epilepsy syndrome with high premature mortality, caused by an *SCN1A* mutation. Biomarkers associated with the risk of sudden cardiac death (e.g., decreased heart rate variability) have been found in patients with this syndrome. In mutant *SCN1A* knock-out mice, postictal bradycardia and seizure-triggered ventricular fibrillation have been recorded before a death resembling SUDEP.[6]

ASMs that affect sodium channels may influence cardiac excitability and conduction, but clinically relevant arrhythmias are usually related to ASM overdose. Long-term ASM use has been associated only rarely with significant cardiovascular complications. A prolonged PR interval is seen in patients on lacosamide and carbamazepine. Symptomatic arrhythmias have been reported in patients receiving lacosamide and carbamazepine in therapeutic dosages, but underlying cardiac abnormalities or the use of multiple sodium channel-blocking ASMs usually (but not always) have been present. Shortening of the QT interval is seen in patients on rufinamide. Routine electrocardiograms should be considered in all patients started on these ASMs and in all patients with pre-existing cardiac arrhythmias.[7]

Anticonvulsant agents may also interact with certain cardiac medications. The concomitant use of phenytoin and quinidine may increase ectopy in patients with ventricular arrhythmias. The metabolism of quinidine, digoxin, lidocaine, and mexiletine may be increased by phenytoin and phenobarbital because of induction of hepatic microsomal enzymes. Amiodarone increases phenytoin levels, and calcium-channel blocking agents, such as verapamil, may increase serum carbamazepine concentrations. For these reasons, serum ASM levels and cardiovascular function should be followed closely when either antiseizure or cardiac medications are introduced or altered.

SEIZURES IN CRITICALLY ILL PATIENTS

Nonconvulsive Seizures and Status Epilepticus

Acute symptomatic seizures in patients who are critically ill are detected typically on continuous EEG monitoring, may have subtle or no clinical signs, and are probably under-recognized. The published incidence of seizures in critically ill patients is highly variable but is nonetheless impressive, ranging from 8 percent to as high as 48 percent in various studies. The possibility of nonconvulsive seizures and status epilepticus should be suspected in any critically ill patient with altered mental status of unknown cause. Subtle motor activity, such as rhythmic twitching of the fingers or eye movements, should raise suspicion of seizure activity in this setting. Diagnosis depends on the EEG findings. Prompt recognition and treatment are essential because delay is associated with a poor outcome.

Continuous EEG monitoring of brain function in critically ill patients usually includes simultaneous video recording and quantitative analysis of EEG trends (Fig. 57-1). The guideline recommendation of the American Clinical Neurophysiology Society for recording for at least 24 to 48 hours using continuous EEG enables the identification of 80 to 95 percent of patients with nonconvulsive seizures.[8] Monitoring should be initiated as soon as possible when nonconvulsive seizures are suspected, and is required in newly admitted critically ill patients with altered mental status and observed seizures.

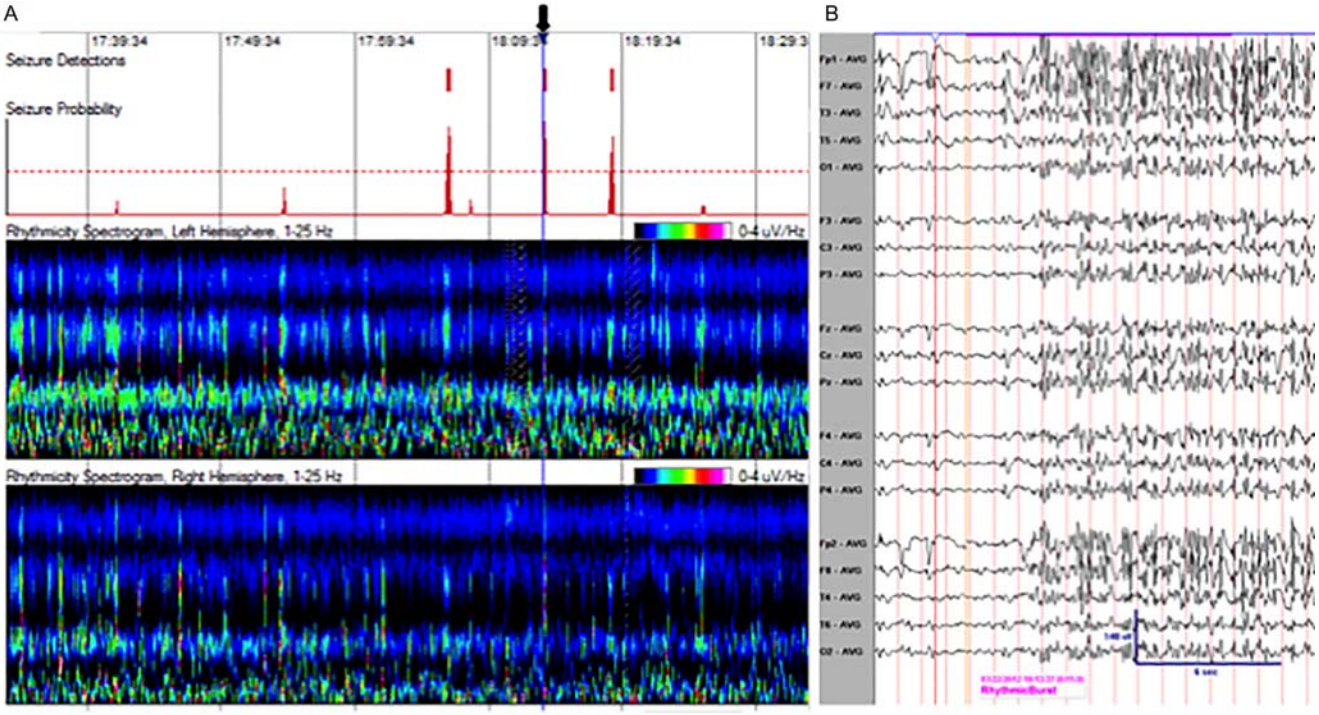

FIGURE 57-1 ■ *A*, Quantitative EEG. EEG for 1 h in a young man intubated for respiratory failure with symptomatic generalized epilepsy and subtle tonic seizures. The upper two panels use a proprietary algorithm to calculate the probability of seizures over time (Persyst seizure detection, Persyst Corporation, San Diego, CA). The lower two panels show time along the *x*-axis, frequency on the *y*-axis (0–25 Hz) and EEG on a color scale. Most power is in the delta range for most of the tracing. There is an asymmetry in faster frequencies, increased over the left hemisphere. Intermittent bursts of power in higher frequencies represent brief electrographic seizures, with subtle or no clinical correlate on video. *B*, EEG recorded using an average reference and corresponding to the arrow in *A*.

Treatment of Seizures in Critically Ill Patients

When evaluating the causes of seizures in critically ill patients, various metabolic derangements must be considered; if detected, therapy is directed at their correction. The electrolyte abnormalities contributing most frequently to seizures are reviewed in a later section. Reversible causes, such as medications (or acute withdrawal of them, including anticonvulsants, benzodiazepines, and barbiturates) and substance abuse are important (Table 57-3).

When ASM treatment is necessary, the increased potential for complex drug interactions in patients receiving numerous other medications and the possibility of altered pharmacokinetics (e.g., due to renal or hepatic impairment) and of adverse systemic effects must be considered. For example, in hypoalbuminemic patients, it may be necessary to monitor free drug levels when using a first- or second-generation ASM (e.g., phenytoin) that exhibits significant serum protein binding. Many first- or second-generation ASMs that are inhibitors or inducers of certain metabolic enzymes may also affect the serum concentration of other medications taken concurrently.

Ideally, ASMs should initially be administered parenterally as loading doses to attain therapeutic serum concentrations, especially in patients with gastrointestinal dysfunction, so limiting the selection of ASMs to those with intravenous formulations.

The use of continuous renal replacement therapy (CRRT) in critically ill patients complicates the use of the third- and fourth-generation ASMs, as most of these are cleared renally. There are as yet no data available for ASM dosing in patients on CRRT. For this reason, ASMs with readily measured serum levels are preferred to guide dosing in patients on CRRT. In general, an ASM that is eliminated renally or affected by dialysis will be removed using CRRT, but the degree of removal will depend largely on the replacement parameters and the specific ASM.

The use of extracorporeal membrane oxygenation (ECMO) is also increasing in critically ill patients, but as for CRRT, no data are available for evaluating specific ASM dosing. The biggest impact of ECMO on drug

TABLE 57-3 ■ Common Medications That May Lower Seizure Threshold

Class	Examples	Notes
Antimicrobials		
β-Lactams	Penicillins, cephalosporins, carbapenems	β-Lactams interact with the $GABA_A$ receptors, interfering with inhibitory effects of GABA in a concentration-dependent manner.
Antituberculous agents	Isoniazid	Isoniazid inhibits pyridoxine phosphokinase, the enzyme that converts pyridoxine for the synthesis of GABA from glutamate, reducing GABA. Give pyridoxine and benzodiazepine.
Antimalarials	Mefloquine, chloroquine	
Fluoroquinolones	Ciprofloxacin	May inhibit the $GABA_A$ receptor; seizures are rare but have been reported.
Analgesics		
Opioids	Morphine, tramadol, codeine, fentanyl	All opioids appear capable of lowering the seizure threshold.
Methylxanthines	Theophylline, aminophylline	Interacts with adenosine A1-receptor; also interferes with activity of BZD.
Antipsychotics	Clozapine (and to a lesser extent, other antipsychotics including risperidone, olanzapine)	Seizures affect 3–6% of clozapine-treated patients.
Antidepressants	Buproprion	A recent systematic review found no evidence for an increase in seizure frequency with other classes of antidepressants. Seizures may be seen in toxicity with other antidepressants.
Antiseizure medications	All	Most can induce paradoxical seizures in overdose; carbamazepine and oxcarbamazepine can exacerbate generalized epilepsies. Stopping them without taper seems invariably to lower seizure threshold.

BZD, benzodiazepines; GABA, γ-aminobutyric acid.
Adapted from Hitchings AW: Drugs that lower the seizure threshold. Adverse Drug React Bull 298:1151, 2016.

dosing lies in the propensity for the ECMO circuit to sequester drugs, resulting in a larger than expected volume of distribution. This phenomenon may decrease over time with continued dosing due to saturation of binding sites. In general, medications with higher volumes of distribution/lipophilicity and higher protein binding tend to be sequestered more. Patients on ECMO frequently receive concomitant CRRT, further complicating dosing. For these reasons, ASMs that have readily available serum levels are strongly preferred.

Seizures Caused by Anoxic-Ischemic Encephalopathy

A high proportion of patients who have been resuscitated after a cardiac arrest go on to develop seizures due to global anoxic-ischemic cerebral injury. Seizures typically commence within 24 hours of cardiopulmonary arrest and may consist of generalized tonic-clonic, tonic, myoclonic, or partial seizures, as well as tonic-clonic or myoclonic status epilepticus. Electrographic status epilepticus with restricted clinical manifestations (usually limited to extraocular or facial muscles) is also well described after cardiopulmonary arrest, occurring in 12 to 22 percent of patients, but may be difficult to recognize.

Published guidelines have emphasized the importance of neurocritical care for patients with brain injury after cardiac arrest, including EEG monitoring for the detection and treatment of seizures.[9] Certain EEG patterns are associated with poor outcome. Thus, generalized background suppression to 20 μV, a burst-suppression pattern with generalized epileptiform activity, or generalized periodic complexes on a flat background are strongly but not invariably associated with poor outcome.[10]

The occurrence of focal seizures or even of generalized tonic-clonic status epilepticus does not determine the eventual clinical outcome of patients in postanoxic coma. By contrast, myoclonic status epilepticus (defined as spontaneous, repetitive, unrelenting, generalized multifocal myoclonus in comatose patients) seems invariably associated with poor outcome and may well represent a marker of severe anoxic-ischemic brain injury. Although hypothermia has antiseizure effects, seizures in resuscitated patients after cardiac arrest may occur during therapeutic hypothermia and, in many patients with nonconvulsive status epilepticus, seizures first appear on EEG during therapeutic hypothermia.

The available evidence does not support the use of prophylactic ASMs in these patients. The same ASMs used for the treatment of status epilepticus from other causes may be considered for seizures and status epilepticus after cardiac arrest, but bearing in mind the potential cardiac effects of selected ASMs reviewed earlier. The neurologic complications of anoxic-ischemic encephalopathy are reviewed in detail in Chapter 9.

INFLAMMATORY AND AUTOIMMUNE DISEASES AND EPILEPSY

Limbic Encephalitis

Limbic encephalitis is the prototype for an autoimmune disease presenting with acute neurologic symptoms, including seizures. Clinical features include the subacute onset of impaired short-term memory, confusion, hallucinations, and sleep disturbances; patients are anxious, irritable, or paranoid. Seizures are not always the presenting symptom but are seen in nearly all cases during the acute or early stages of the illness. They usually do not respond to ASMs. Diagnosis is by autoantibodies to intracellular antigens or extracellular (cell surface) antigens involved in synaptic transmission (Table 57-4). Paraneoplastic etiologies for limbic encephalitis must be excluded. These syndromes are discussed in detail in Chapter 27.

TABLE 57-4 ■ Antigens for Autoantibodies Associated With Seizures

Intracellular Antigens
ANNA-1, CRMP-5, GAD65, Ma-2
Extracellular Antigens (Cell Surface or Synapse)
AMPA receptor, $GABA_B$ receptor, ganglionic ACh receptor, NMDA receptor, VGKC complex (Caspr2, Lgi1)

ACh, acetylcholine; ANNA-1, antineuronal nuclear antibody-type 1; Caspr2, contactin-associated protein-like 2; CRMP-5, collapsing response-mediator protein 5; $GABA_B$, γ-aminobutyric acid subtype B; GAD65, glutamic acid decarboxylase 65; Lgi1, leucine-rich glioma inactivated 1; NMDA, N-methyl-D-aspartate; VGKC, voltage-gated potassium channel antibody.

Selected autoimmune encephalopathies have characteristic clinical or EEG features that are helpful to recognize. Faciobrachial dystonic seizures are brief (1 to 2 seconds) motor seizures, affecting the limbs and face, that can occur over 100 times per day, do not have an EEG correlate, and typically precede the development of anti-LGI1 encephalitis (i.e., encephalitis with antibodies to leucine-rich glioma inactivated 1). Patients with anti-NMDA (N-methyl-D-aspartate) receptor encephalitis may have a unique EEG pattern termed "extreme delta brush" because of its resemblance to waveforms seen in premature infants.

In the majority ($>70\%$) of patients with limbic encephalitis the associated seizures are successfully treated with immunotherapy and ASMs acutely, and most do not require chronic antiseizure therapy. The risk for developing epilepsy in these patients appears low (10 to 15%) and is dependent on the antigen. Disorders with antibodies to cell membrane antigens (VGKC, NMDA-R, AMPA-R, and GABA) tend to be less severe and complete recovery is possible. Conversely, patients with antibodies to an intracellular antigen (e.g., GAD65) frequently develop epilepsy and have a suboptimal response to treatment.

Connective Tissue Diseases and Cerebral Vasculitis

The connective tissue diseases are discussed in detail in Chapter 50. Of these, systemic lupus erythematosus (SLE) probably has the highest incidence of neuropsychiatric symptoms. Seizures are frequent both at the time of diagnosis and during disease flares, seen in 40 to 85 percent of persons with SLE. The prevalence of epilepsy in the SLE population is also increased, variably reported in larger series from 3 to 29 percent.[11] Neuropsychiatric manifestations imply a poorer prognosis for SLE than otherwise, but the presence of seizures or psychosis without other neurologic features or significant renal disease does not reduce survival.

Seizures in SLE may be due to a hypertensive or metabolic encephalopathy, especially in the context of lupus nephritis and uremia (discussed earlier) or as a complication of immunosuppressive therapy (discussed in the next section on seizures in transplant patients). Seizures in SLE may also reflect direct brain involvement by various antibodies that have been implicated in the pathogenesis of neuropsychiatric SLE. Of these, antiphospholipid antibodies are important as these may have a direct neuromodulatory effect. The frequency of seizures and epilepsy may correlate with the presence of these antibodies, although this is not clear. Cerebral microinfarcts and, less often, subarachnoid and intracerebral hemorrhages are found on pathologic examination and may relate to an immunologically mediated vasculopathy.

Treatment of CNS lupus is discussed in Chapter 50. ASMs are frequently started for a limited period (e.g., 3 months) while immunosuppression is used to treat the SLE flare. Drug-induced lupus may occur with various ASMs (including phenytoin, carbamazepine, valproic acid, and lamotrigine), but there is no evidence that ASMs exacerbate idiopathic SLE.

Cerebral vasculitis or vasculopathy from other causes may lead to seizures. Antiphospholipid antibody syndrome may occur without SLE. In Sjögren or Behçet syndrome, convulsions may be associated with a flare of disease activity. Seizures rarely are described due to cerebral involvement in rheumatoid arthritis, scleroderma, or mixed connective tissue disease. The one exception to this is linear scleroderma with hemifacial atrophy of the face, or Parry–Romberg syndrome, in which intractable epilepsy can be part of the spectrum of disease.

Thyroid Disease and Hashimoto Encephalopathy

Hashimoto encephalopathy is a relapsing encephalopathy occurring in association with Hashimoto thyroiditis, with high titers of antithyroid peroxidase antibodies, antithyroid microsomal antibodies, and antithyroglobulin antibodies. Thyroid hormone levels are usually decreased, but 30 percent of persons may be euthyroid or hyperthyroid. Seizures occur in the majority of these patients. A subset of patients responds to intravenous methylprednisolone (termed steroid-responsive encephalopathy associated with autoimmune thyroiditis, or SREAT). ASMs are required to treat seizures acutely; seizures tend to remit as the encephalopathy improves. The disorder is discussed in detail in Chapter 18.

Inflammatory Bowel Disease

Both ulcerative colitis and Crohn disease are chronic relapsing inflammatory diseases of the gut. They are associated with neurologic and systemic complications, possibly including an increased incidence of epilepsy—but this is not quite clear. The epidemiologic association of celiac disease with epilepsy is clearer, seen in between 3.5 and 5.5 percent of patients with celiac disease.

Diabetes and GAD65 Antibodies

Antibodies to glutamic acid decarboxylase 65-kDa isoform (GAD65) have been found in 2 to 3 percent of adults and 6 to 7 percent of children with chronic epilepsy. GAD65 antibodies also occur in 80 percent of patients with type 1 diabetes (and interestingly, epilepsy is increased in this population compared with controls). Very high titers of GAD65 antibodies are seen in patients with seizures in the context of limbic encephalitis. Compared with GAD65 antibodies in epilepsy or in patients with diabetes, patients with limbic encephalitis have substantially higher titers of serum antibodies (~100 to 1,000 times higher), and the antibodies are detectable in CSF. Patients with epilepsy and GAD65 antibodies show a poor response to immunotherapy and tend to be refractory to medical treatment.

Multiple Sclerosis and Other Demyelinating Diseases

Seizures are occasionally the first presentation of multiple sclerosis. The incidence of seizures in multiple sclerosis is quite low, but varies in different series to as high as 8 percent. One-third of seizures occur in the context of an acute flare of the disease and occasionally present as focal status epilepticus. Seizures usually stop with disease remission. The reason for the occurrence of seizures (a cortical disturbance) in demyelinating disease is not clear, but specialized magnetic resonance imaging sequences demonstrate intracortical lesions in patients with seizures.

Seizures also occur in 11 to 43 percent of patients with acute disseminated encephalomyelitis. Antibodies against myelin oligodendrocyte glycoprotein have been identified in about 40 percent of these patients, but such antibodies are also found in other demyelinating disorders (including clinically isolated syndromes) that do not manifest with seizures. There is no information about the risk of developing epilepsy in these patients.

HEPATIC PORPHYRIAS

Porphyrias are named from the Greek word *porphura*, meaning purple, and this refers to the discoloration of the urine that may be seen due to red and purple pigments produced in these disorders. Porphyrias are caused by deficiencies in enzymes of the heme biosynthetic pathway that lead to the accumulation of heme precursors (porphyrins). The inherited conditions are classified into the acute porphyrias (hepatic porphyrias) and cutaneous (erythropoietic) porphyrias, reflecting the location of the accumulation of porphyrins. Three of the acute porphyrias may present with epilepsy and neuropsychiatric symptoms: acute intermittent porphyria (AIP), hereditary coproporphyria, and variegate porphyria.

AIP is the most common hepatic porphyria, and the most commonly associated with seizures and epilepsy. The clinical features of variegate porphyria are identical to AIP, except for cutaneous photosensitivity that is seen in 30 percent. Persons are asymptomatic until exposed to circumstances that demonstrate the deficiency, including infection, hormonal cycles, diet, and medications. The classic symptoms are due to an acute neuropathy and evolve over hours or days. They include abdominal pain, nausea, vomiting, weakness, and severe neuropathic pain. Laboratory studies demonstrate increased δ-aminolevulinic acid (ALA), and porphobilinogen (PBG) in the urine.

Encephalopathy, coma, or seizures are seen in 5 to 20 percent of persons during acute attacks and may be the presenting feature in AIP. These seizures may reflect a direct neurologic effect of ALA binding to GABA receptors. Defects in hepatic heme synthesis may alter brain levels of neurotransmitters. Seizures may also be symptomatic of metabolic disturbances from excessive vomiting or inappropriate secretion of antidiuretic hormone.

All the enzyme-inducing ASMs, valproic acid, and benzodiazepines may exacerbate or precipitate attacks by stimulating hepatic ALA synthase activity, and ideally these drugs should be avoided. Experimental studies suggest that lamotrigine, felbamate, and topiramate may also exacerbate hepatic porphyrias. These studies are supported clinically in the case of lamotrigine. Gabapentin, pregabalin, and levetiracetam are probably safe and have been used successfully. The use of intravenous benzodiazepines also seems relatively safe despite evidence that they may be porphyrinogenic. If seizures are medically refractory, magnesium sulfate (a noncompetitive NMDA receptor antagonist that may enhance the effect of ASMs) may be used intravenously as an ASM to keep serum magnesium concentrations between 2.5 and 7.5 mmol/L. Urine ALA and PBG levels must be monitored closely during therapy.

SEIZURES IN TRANSPLANT RECIPIENTS

The neurologic complications of organ transplantation are summarized in Chapter 44. Transplant recipients are at high risk for seizures that may relate to their underlying illness, irradiation, or chemotherapy, and to perioperative metabolic abnormalities or complications such as cerebral ischemia. After surgery, the effects of immunosuppression, therapeutic agents, and rejection are also important causes.

Immunosuppressive agents, especially cyclosporine, have been associated with seizures. These may occur with serum levels of cyclosporine within or exceeding the therapeutic range and may relate to a cyclosporine metabolite. Other immunosuppressive agents may also cause post-transplantation seizures. Tacrolimus (FK506) has neurologic complications similar to cyclosporine, including seizures and encephalopathy. The antirejection agent muromonab-CD3 (OKT3) can cause seizures as part of a cytokine encephalopathy. Sirolimus (rapamycin), one of the newer immunosuppressive agents, did not cause seizures or other neurotoxicity in at least one series consisting of kidney and liver transplant recipients. In bone marrow recipients, busulfan, either alone or in combination with cyclophosphamide, may cause seizures.

Seizures may also result from CNS infections or other brain insults (e.g., stroke or cerebral hemorrhage), or from metabolic abnormalities including hyponatremia, hyperosmolar states, hypoglycemia, or multiorgan system failure. Finally, transplant rejection may lead to an encephalopathy syndrome that includes seizures, sometimes as the first manifestation of rejection.

Options for ASMs in transplant recipients are constrained by the type of transplantation procedure undergone by the patient and the immunosuppressive drugs in use. Valproic acid is contraindicated in liver recipients because of its potential hepatotoxicity. Carbamazepine should not be used in bone marrow recipients because it may cause myelosuppression. Bone marrow engraftment occurs 2 to 6 weeks after transplantation, and phenytoin, phenobarbital, and valproic acid are best avoided over this period in favor of a newer ASM. The enzyme-inducing first- and second-generation ASMs may affect the metabolism of immunosuppressive agents. Thus, the clearance of cyclosporine and corticosteroids is increased by phenobarbital, phenytoin, and carbamazepine, necessitating increased dosages of corticosteroids by 25 to 30 percent and of cyclosporine depending on serum cyclosporine levels.

Levetiracetam does not appear to influence immunosuppressive drug levels and is not hepatically metabolized. There seems to be a consensus that levetiracetam is a good initial choice for ASM therapy in all transplant populations. Gabapentin may also be a reasonable choice in liver transplant recipients (not hepatically metabolized), but in practice is not used.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND SEIZURES

Seizures occur in perhaps 10 percent of persons infected with human immunodeficiency virus (HIV). They may occur at any stage of HIV infection or acquired immunodeficiency syndrome (AIDS) and are sometimes the presenting symptom of HIV infection. Involvement of the nervous system is present at autopsy in 85 percent of persons with HIV infection. The introduction of combination antiretroviral therapy using protease inhibitors has reduced brain involvement by opportunistic infections in these autopsy series, but also corresponds to an increase in HIV encephalopathy of from 34 to 60 percent, perhaps reflecting the dramatic improvement of survival in patients with HIV infection. Variants of HIV encephalitis with intense perivascular inflammation have also emerged, presumably due to an exaggerated response from a reconstituted immune system.

In nearly half of patients with HIV/AIDS and seizures, no cause except HIV infection is found and in these persons direct cerebral HIV infection seems the correct explanation. Other important CNS disorders that may be responsible and are associated with HIV/AIDS include CNS toxoplasmosis, cryptococcal meningitis, neurotuberculosis, progressive multifocal leukoencephalopathy, and CNS lymphoma. Systemic illness, alcohol or drug use (especially cocaine), and even antiretroviral agents are also important causes of acute symptomatic seizures. A detailed diagnostic evaluation is therefore required when HIV-infected patients experience the new onset of seizures.

The risk for subsequent seizures following a first one is relatively high in HIV-infected persons, and for this reason ASMs are usually started following a first seizure. The use of newer ASMs that do not induce hepatic enzymes is preferable as first-line therapy. On balance, the older enzyme-inducing antiepileptic agents are best avoided in patients with HIV/AIDS due to concern for drug–drug interactions. For example, phenytoin interacts with protease inhibitors, affecting viral load, and may cause intoxication in patients treated concurrently with fluconazole, commonly prescribed in AIDS patients.

SEIZURES ASSOCIATED WITH SYSTEMIC CANCER

Seizures are a relatively common neurologic complication of systemic cancer in children and adults. Different potential etiologies must be considered when seizures occur in this context. First, seizures may be due to direct brain effects including CNS metastasis in 10 to 20 percent of persons with systemic cancer. Metastases are especially frequent for melanoma, lung, breast, renal cell, gastrointestinal, and germ cell tumors, as well as when leptomeningeal seeding occurs by malignant tumor cells (carcinomatous meningitis). Guidelines for the treatment of patients with single metastatic lesions recommend surgery (if possible) followed by whole-brain radiation therapy.[12] In patients operated for CNS metastases but who have never had seizures, ASMs are recommended perioperatively for 7 days only (levetiracetam is preferred for this by neurosurgical services) and then discontinued.

Second, seizures may be symptomatic of an associated diagnosis or condition occurring as a consequence of the systemic cancer. Examples include stroke due to hypercoagulable states or nonbacterial thrombotic endocarditis. CNS infections, including fungal or parasitic abscesses, may result from immunosuppression after chemotherapy and produce seizures.

Third, seizures are an uncommon but described complication of chemotherapy, including etoposide, L-asparaginase, alkylating agents such as chlorambucil or busulfan, immunotherapies, methotrexate, and cytosine arabinoside.

Fourth, acute seizures may be secondary to cancer-related metabolic disturbances, paraneoplastic encephalitis, or drugs used to treat complications, such as pain medications and antibiotics.

In patients who have had a seizure and are considered to be at increased risk for future seizures, ASMs should be started. There are no specific recommendations regarding the type of ASM, dose, or length of therapy.[13] Chemotherapy used to treat systemic cancers may complicate the selection of an ASM. For example, corticosteroids are indicated for patients with symptoms secondary to elevated intracranial pressure. Phenobarbital and phenytoin shorten the half-life of corticosteroids, and increased or decreased serum concentrations of phenytoin have been described in patients receiving corticosteroids. A second concern is that many chemotherapeutic agents undergo hepatic metabolism or induce or interfere with hepatic enzymes. Consequently, first- and second-generation ASMs that induce hepatic enzymes may lower the effectiveness of cancer chemotherapy. Because of the potential for drug–drug interactions, ASMs that do not induce hepatic enzymes, including levetiracetam, gabapentin, pregabalin, or lacosamide, are preferred in individuals undergoing cancer chemotherapy.

ENDOCRINE OR METABOLIC DISORDERS

Disorders of Glucose Metabolism

Abnormal glucose levels, whether too high or too low, can cause seizures. Experimental studies suggest that a threshold glucose concentration is necessary to support synaptic transmission and that elevated extracellular glucose levels are associated with neuronal hyperexcitability. The problem is especially pertinent to individuals with diabetes, whose blood glucose levels can fluctuate widely over the course of a day as a result of intercurrent illness, variations in insulin levels, or other metabolic factors.

Hypoglycemia must be considered and excluded as a possible cause in any patient with seizures. It is treated by intravenous administration of dextrose and correction of any other metabolic abnormalities. Patients usually do well but are best hospitalized for observation because hypoglycemia may recur hours after initial treatment.

Seizures are also relatively common in nonketotic hyperglycemia and may be of any type. They are typically refractory to ASMs but respond to correction of hyperglycemia with insulin and intravenous fluid replacement. Associated focal neurologic abnormalities are usually transient, and recovery is typically complete if treatment is initiated before coma occurs. ASMs are not indicated for seizures related to nonketotic hyperglycemia. Phenytoin must specifically be avoided because it can exacerbate hyperglycemia by inhibiting insulin release.

Thyroid Disease

Seizures are not uncommon in hypothyroidism, are usually generalized, and remit with treatment of the hypothyroidism. ASMs such as phenytoin and carbamazepine may reduce serum thyroxine and triiodothyronine levels because of competition for serum-binding proteins; however, patients remain clinically euthyroid because free thyroxine and triiodothyronine fractions are increased.

Seizures are uncommon in thyrotoxicosis, but hyperthyroidism or excess thyroxine may occasionally cause seizures or exacerbate pre-existing epilepsy. When seizures occur in the setting of thyrotoxicosis, the hyperthyroid state should be corrected; ASMs usually are not required except occasionally in the acute setting.

Disorders of Sodium Homeostasis

The neurologic manifestations of disorders of sodium homeostasis are reviewed in Chapter 17. Symptoms reflect the rate of development of hyponatremia rather than absolute serum sodium levels, and chronic hyponatremia is surprisingly well tolerated. Seizures are usually seen in the context of acute hyponatremia with concentrations less than 115 mEq/L, but seizures may occur at higher levels if the decrease is rapid. Children are at high risk for cerebral edema in hyponatremia. Both partial and generalized seizures may occur.

Seizures in hyponatremia require careful correction using intravenous hypertonic (3%) saline, and increases in serum sodium concentration cannot exceed 1 mmol/L (1 mEq/L) per hour or 12 mmol/L (12 mEq/L) over 24 hours. More rapid correction of hyponatremia may cause osmotic demyelination (previously termed pontine and extrapontine myelinolysis), as well as seizures due to too rapid correction.

Hypernatremia if severe (>160 mEq/L) causes an encephalopathy. The aim of treatment is to replace body water. Seizures may occur, especially during rehydration.

Calcium and Magnesium Imbalance

The neurologic manifestations of hypocalcemia are reviewed in Chapter 17. Hypocalcemic seizures are quite common, affecting 30 to 70 percent of patients with hypoparathyroidism, often accompanied by an altered sensorium and tetany. Treatment of hypocalcemic seizures involves correction of serum calcium levels and treatment of any underlying cause. Hypercalcemia only infrequently causes seizures.

Seizures may also be provoked by hypomagnesemia, especially when the serum magnesium concentration decreases below 0.8 mEq/L (see Chapter 17). Convulsions in such circumstances are treated with

TABLE 57-5 ■ Proposed Cut-Off Values in Biochemical Parameters in Patients With Symptomatic Seizures from Common Metabolic Disorders

Biochemical Parameter	Cut-Off Value
Serum glucose	>450 mg/dL associated with ketoacidosis whether or not diabetes exists
Serum sodium	<115 mg/dL
Serum calcium	<5.0 mg/dL
Serum magnesium	<0.8 mg/dL
Serum urea nitrogen	>100 mg/dL
Plasma creatinine	>10.0 mg/dL

Adapted from Beghi E, Carpio A, Forsgren L, et al: Recommendation for a definition of acute symptomatic seizure. Epilepsia 51:671, 2010.

intravenous magnesium; calcium gluconate should be available to counteract transient hypermagnesemia. Seizures are not seen in hypermagnesemia (Table 57-5).

SEIZURES RELATED TO ALCOHOL, MEDICATIONS, AND RECREATIONAL DRUGS

Alcohol

Seizures are a common consequence of alcohol use, as discussed in Chapter 33. Alcohol potentiates the activity of $GABA_A$ receptors, and chronic alcohol use results in a compensatory downregulation of these receptors. As a consequence, when alcohol is stopped, neuronal inhibition is decreased and this can result in seizures. Usually, alcohol-related seizures are self-limited generalized convulsions that happen within 48 hours after stopping alcohol, often accompanied by other signs and symptoms of alcohol withdrawal. Convulsive status epilepticus may occur uncommonly after alcohol withdrawal. The brain substrates responsible for these seizures are largely in the brainstem, and the ASMs effective for generalized epilepsies seem to be the most helpful in this context. In the United States, benzodiazepines are preferred to treat alcohol withdrawal and to prevent seizures.[14]

Patients with seizures solely in the setting of alcohol or drug abuse do not, by definition, have epilepsy. Because seizures are self-limited, long-term ASM therapy is not indicated. These patients should be advised against chronic alcohol use or binge drinking.

Cocaine and Other Recreational Drugs

Seizures may be induced by acute intoxication with recreational drugs, especially cocaine and other stimulants. Less frequently, seizures may appear as a withdrawal phenomenon. Seizures are typically convulsions and do not require acute or chronic treatment with ASMs.

Between 2 and 8 percent of patients presenting to the emergency department for cocaine toxicity will also have seizures, usually generalized convulsive in type. This risk is highest with intravenous or inhaled crack cocaine and may reflect a direct CNS stimulant effect through blockage of neurotransmitter reuptake at dopaminergic and noradrenergic nerve terminals. Other proposed mechanisms include a kindling effect with chronic use, cerebrovascular or systemic effects, or a terminal event in massive cocaine overdose.

Amphetamines are an uncommon cause of generalized convulsions; as for cocaine, this happens more commonly after intravenous use and administration of high doses. Seizures are also uncommon with phencyclidine. Heroin use has been associated with convulsions, although this may relate to anoxia and chemical adulterants rather than to a convulsant effect of heroin itself.

Complications of intravenous drug abuse that may cause seizures, including infectious endocarditis and HIV infection, should be sought in patients with convulsions associated with the use of heroin or other intravenous drugs. Marijuana is often used concurrently with heroin and other recreational drugs but seems independently to lower the risk of a first seizure.

Medications

ANTIDEPRESSANT DRUGS

The most commonly implicated drugs in causing seizures are the tricyclic antidepressants (TCAs) and bupropion. The absolute risk of TCAs at usual therapeutic doses is actually quite low, but overdose may cause seizures. Bupropion is a monocyclic inhibitor of dopamine and has a clear dose-related risk of seizures, with a seizure incidence of 0.4 percent at doses of 450 mg/day or less, increasing to 2.2 percent at doses exceeding 450 mg/day. Conversely, selective serotonin reuptake inhibitors (SSRIs) appear to have low seizure risk even in overdose, with no seizures in a series of 234 cases of fluoxetine overdose. The seizure risk with SSRIs is generally quoted as 0.2 percent, based on premarketing data for sertraline. Importantly, antidepressants as a class may actually reduce the risk for seizures compared to placebo, consistent with the observation that low levels of pre/postserotonergic transmission in depressed persons may be a risk factor for seizures.

Antipsychotics and Lithium

Clozapine, an atypical antipsychotic, demonstrates a clear dose-related risk of seizures of 0.9 percent for doses less than 600 mg/day and 1.5 percent for higher doses, and has the highest seizure risk of all the antipsychotic medications. An increased risk of seizures has also been reported with olanzapine and quetiapine, but the other atypical antipsychotics (ziprasidone, aripiprazole, and risperidone) as a group do not seem to be associated with an increased incidence of seizures. Seizures with lithium intoxication are common when levels exceed 3.0 mEq/L although seizures have been reported in patients on lithium at therapeutic levels.

Antibiotics

Seizures have been reported with penicillins, cephalosporins, carbapanems (β-lactam antibiotics), and fluoroquinolones. They are believed to be due to direct or indirect binding to $GABA_A$ receptors. Of these antibiotics, the risk is highest for imipenem, from 0.2 to 0.9 percent, although acute seizures were seen in one series in 11 of 200 patients on imipenem. Risk is increased in the very young or very old and with renal insufficiency, focal neurologic deficits, and severity of illness, and when given intravenously or intrathecally.

Other Medications That May Cause Seizures

Tramadol is a weak μ-opioid receptor agonist that also induces serotonin release and inhibits the reuptake of norepinephrine. Seizures have been reported with tramadol at therapeutic doses, but are very frequent at supratherapeutic levels, seen in 14 percent of overdoses in one series.

Isoniazid is a common cause of drug-induced seizures, particularly in intentional overdose, believed to be due to inhibition of pyridoxine (vitamin B_6) metabolism that is required to synthesize GABA. For this reason, isoniazid-induced seizures may be refractory to ASMs and should be treated with intravenous pyridoxine.

Seizures may result from theophylline. This is most likely due to the inhibition of phosphodiesterase, which may reduce adenosine-mediated CNS inhibition. Status epilepticus may be seen in acute overdose; it does not respond to ASMs and requires hemodialysis or hemoperfusion therapy. Theophylline is best avoided in persons with epilepsy for these reasons.

Seizures have been reported with the anesthetic agents propofol, sevolfurane, and lidocaine. Propofol, which acts on the $GABA_A$ receptors and is used in the treatment of refractory status epilepticus, has also been associated with seizures during induction or recovery from anesthesia. Seizures can occur in the setting of abruptly stopping benzodiazepines and barbiturates, and also baclofen, which may cause nonconvulsive status epilepticus.

CEREBRAL TRAUMA, SEIZURES, AND EPILEPSY

Traumatic brain injuries (TBIs) are an important cause of seizures and epilepsy, especially in young adults, and may also increase seizures in persons with pre-existing epilepsy. Seizures caused by TBI are classified as immediate (at the moment of injury, or within minutes), early (within the first 7 days), and late (beyond the first week after injury). The incidence of immediate seizures following TBI is 1 to 4 percent; they are usually generalized convulsions and do not imply that the patient will develop epilepsy. Conversely, early seizures (occurring more than 1 hour after injury) do seem to present an increased risk of post-traumatic epilepsy. These seizures are symptomatic for the physics of the initial brain injury, including shearing injury to fiber tracts and blood vessels, bleeding, and brain swelling. The incidence of early seizures (within the first 7 days) is 2 to 9 percent, depending on the severity of the brain injury.[15]

The latency from the initial TBI to a first unprovoked seizure can be up to several years. Approximately 80 percent of patients with post-traumatic epilepsy experience their first (late) seizure within the first 12 months after injury and more than 90 percent do so before the end of the second year. However, the risk for a first late seizure is increased more than 10 years after the traumatic event. The presence of early seizures is the most important risk factor for the development of late seizures and epilepsy, and the incidence for late seizures in persons with early seizures is high, from 25 to 75 percent. Other risk factors include open or penetrating brain injury, focal lesions (hematoma, contusion) or neurologic signs, and prolonged coma or amnesia. The EEG is disappointing as a predictor of the risk for development of post-traumatic epilepsy, as many patients who eventually develop post-traumatic epilepsy have normal recordings early after injury. MRI of the brain is the imaging modality of choice, and has shown some promise for improving prediction of post-traumatic seizure risk.[15]

The precise mechanisms of epileptogenesis that leads to late seizures are poorly understood. Treatment of early-onset seizures with ASMs decreases early seizures, but prospective clinical trials have failed to demonstrate that preventing early seizures using ASMs affects mortality, morbidity, or the development of late epilepsy. These include randomized or quasi-randomized monotherapy studies using phenytoin, phenobarbital, carbamazepine, and valproic acid. Glucocorticoids also appear to have no benefit in preventing the development of seizures after TBI.

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CHAPTER

58

Movement Disorders Associated With General Medical Diseases

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CHOREA, BALLISM, AND DYSTONIA
- Hypoxic-Ischemic Disorders
  - *Stroke*
  - *Global Hypoxia-Ischemia*
- Toxins
- Drug-Induced Dystonia and Chorea
- Infectious Disorders
  - *Bacterial Infections*
  - *Viral Infections*
  - *Fungal and Parasitic Infections*
- Autoimmune, Inflammatory, and Paraneoplastic Disorders
- Metabolic Disorders
- Other Causes
- Approach to Diagnosis
- Treatment

MYOCLONUS
- Hypoxia-Ischemia
  - *Stroke*
  - *Global Hypoxia-Ischemia*
- Metabolic Disorders
- Autoimmune and Inflammatory Disorders
- Drug- and Toxin-Induced Myoclonus
- Paraneoplastic Disorders
- Infections
- Injury by Physical Agents
- Approach to Diagnosis
- Treatment

TREMOR
- Stroke
- Medications
- Toxins and Recreational Agents
- Metabolic Disorders
- Infections
- Immune Disorders
- Other Causes of Tremor
- Approach to Diagnosis
- Treatment

PARKINSONISM
- Vascular Causes
- Medications and Bone Marrow Transplantation
- Toxins
- Metabolic Disorders
- Infections
- Autoimmune and Paraneoplastic Disorders
- Trauma
- Other Causes of Parkinsonism
- Approach to Diagnosis
- Treatment

Movement disorders may complicate a variety of general medical diseases. Evaluation of patients with involuntary movements or postures requires a detailed history, including an account of perinatal events, ethnicity, parental consanguinity, psychiatric disorders, past medications, exposure to infectious agents, immunologic status, substance abuse, and exposures to toxins. The age of onset and pattern of progression further direct the evaluation. Clinical examination should be directed at determining the character and distribution of the abnormal movements and excluding non-neurologic causes.

CHOREA, BALLISM, AND DYSTONIA

Dystonia or chorea occurs in a wide variety of medical contexts. Although chorea is typically a more fluid, “dance-like” undulation of a limb, and dystonia is a slower movement or a sustained abnormal posture of a limb or the trunk, it is sometimes difficult to distinguish between them. Many cases of dystonia or chorea are secondary to a neurodegenerative disorder or an hereditary metabolic defect, which are not the subject of this review. The focus here is on movement disorders (other than ataxias) that arise in the context of a systemic medical disorder.

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In a series of 51 cases of chorea from Italy, vascular causes were identified in 40 percent, drug-induced causes in 14 percent, acquired immunodeficiency syndrome (AIDS)–related causes in 10 percent, Huntington disease in 10 percent, hyperglycemia in 4 percent, and hyponatremia in 4 percent; single cases (2% each) of borreliosis (Lyme disease), Sydenham chorea, and acanthocytosis were also identified.[1] The epidemiology will differ in regions where AIDS or other infectious conditions are more prevalent.

Chorea is usually associated with dysfunction of the thalamus or basal ganglia. In most cases, the physiologic effect of the disorder reduces inhibitory input from the globus pallidus interna to the motor thalamus, resulting in excessive thalamocortical motor facilitation.

Dystonia is characterized by impaired inhibition at multiple levels of the central nervous system (CNS), and altered levels of several neurotransmitters have been reported in various diencephalic nuclei, as well as the putamen, globus pallidus, red nucleus, and subthalamic nucleus. Nonetheless, the generation of dystonia remains poorly understood.

Hypoxic-Ischemic Disorders

Chorea and dystonia due to hypoxia-ischemia may result from global or focal cerebral hypoperfusion as well as cellular hypoxia, such as in mitochondrial toxicity.

STROKE

Stroke may cause a variety of movement disorders depending on the location of the lesion and age of the patient. The abnormal movements may develop during the acute phase of a stroke or after a variable delay, and can be transient or permanent. Dystonia, especially, is rare in the acute phase but tends to occur at a time when patients are recovering from the initial motor deficit.

In a series of 1,500 patients with stroke, Alarcon and colleagues found that movement disorders occurred in about 56 (approximately 4%) over the following year; chorea occurred in 20, whereas dystonia, tremor, and parkinsonism were less common, occurring in 16, 14, and 6, respectively.[2] The average age at onset of chorea was 75 years, whereas that for dystonia was 48. Patients with deep (rather than isolated surface) vascular lesions were more likely to develop a movement disorder. *Hemichorea* occurred most commonly with contralateral thalamic strokes but also occurred with other lesions of the basal ganglia (putamen and subthalamic nucleus), white matter tracts (corona radiata, internal and external capsule), and pons. *Hemiballism* was caused most often by a lesion of the contralateral subthalamic nucleus but also occurred with lesions of the frontal and parietal lobes or the corona radiata. Putamenal strokes caused *focal* or *hemidystonia* most frequently, although lesions of the pons or globus pallidus and larger strokes of the frontal or parietal lobe were also sometimes responsible.

Thus, lesions in different parts of the brain may produce the same movement disorder, perhaps because they are interrupting the same motor networks but at different levels. The time to onset of the movement disorder is shorter for chorea—usually within 1 week of the stroke—than for dystonia and tremor, which typically developed 2 to 3 weeks after the stroke in the study by Alarcon and associates.[2] Hemorrhagic strokes are responsible for many movement disorders developing after 6 months or more, and especially for dystonia developing in young patients.[3] Most patients with these poststroke movement disorders improve over time.

Various points deserve emphasis. Severe pathologic involvement of the basal ganglia, as by an infarct, does not always lead to the development of a movement disorder, and many movement disorders relate to diffuse changes at multiple rather than single sites. A movement disorder may emerge immediately or soon after a stroke or—particularly with vascular parkinsonism—after many months or years, and can be progressive, evolving in severity and also in the character of the abnormal involuntary movements. The pathophysiologic basis of this progression is unclear.

Treatment is symptomatic. Chorea or ballismus may respond to tetrabenazine, deutetrabenazine, or valbenazine, or to haloperidol or other neuroleptics, and there are anecdotal reports of benefit with clonazepam, topiramate, and valproate. In severe and refractory cases, ablative surgery or deep brain stimulation may be indicated. Poststroke dystonia may respond to tetrabenazine, anticholinergic drugs, benzodiazepines, or baclofen. Botulinum toxin may help focal and segmental dystonias. Severe hemidystonia may be helped by deep brain stimulation of the globus pallidus or thalamus.

GLOBAL HYPOXIA-ISCHEMIA

The time course of a movement disorder resulting from global hypoxic-ischemic injury differs in infants, children, and adults. In infants and children, the movement disorder takes longer to develop and the abnormal movements are more likely to generalize. In adults, chorea or dystonia becomes manifest as any hemiparesis resolves and usually remains localized. Only in young children with postpump chorea and adults with postthalamotomy syndrome does the movement disorder commonly begin within a week of injury. The basis of such differences is not clear.

The age of patients at the time of anoxia influences the outcome. Patients developing an akinetic-rigid parkinsonian syndrome are typically in middle or later life, whereas those developing pure dystonia are usually younger than 20 years. The site of injury is also important. Involvement of the putamen is more likely to cause dystonia, whereas lesions of the globus pallidus are usually associated with parkinsonism. Perinatal hypoxic-ischemic injury may lead to any pattern of dystonia, often after a long interval. At onset the dystonia is focal or, rarely, segmental, and commonly spreads over a variable period that may be as short as a few months or as long as 20 to 30 years, resulting in segmental dystonia, hemidystonia, or generalized dystonia.

Postoperative encephalopathy with chorea, also known as *postpump chorea*, consists of chorea, athetosis, or ballismus, episodic eye deviations, and hypotonia. It occurs in infants or children within 12 days of cardiac surgery involving hypothermia, cardiopulmonary bypass, and often complete circulatory arrest, and may be severe. Although this surgical complication was previously common, occurring in up to 20 percent of children, current techniques have drastically reduced its incidence. Risk factors include age at time of surgery (higher risk between 6 months and 5 years), rapid cooling during cardiopulmonary bypass, lower body temperature, and the duration of hypothermic circulatory arrest. Infants younger than 6 weeks are less susceptible; in older infants, the chorea is often mild and reversible. The pathophysiology is poorly understood, although it seems likely that hypoxic-ischemic mechanisms secondary to surgical technique (including deep hypothermia) play a role.

Children and young adults sustaining acute hypoxic injury may also develop dystonia. They usually have focal or unilateral findings clinically and on imaging studies, despite the global insult. Dystonia may develop after 1 week to 3 years and typically generalizes over the following months or years; imaging shows abnormalities especially in the putamen.

Polycythemic chorea occurs for uncertain reasons. Polycythemia rubra vera has a male predominance, but polycythemic chorea is more common in women. Neurologic manifestations of polycythemia are common, occurring in 50 to 80 percent of patients, and include headache, vertigo, stroke, visual symptoms, tinnitus, and paresthesias. Chorea is a rare complication, occurring in 0.5 to 5 percent of patients. Examination may also show a plethoric complexion and splenomegaly. The chorea may be the presenting symptom of polycythemia, may begin suddenly or gradually, is sometimes episodic, and typically becomes generalized but affects particularly the facial, lingual, and brachial muscles. The limbs are hypotonic, with pendular patellar tendon reflexes. The chorea may persist for up to several years, with spontaneous remissions and recurrences. Treatment is of the underlying polycythemia but additional symptomatic control with dopamine-depleting or dopamine-blocking agents may be necessary.

Toxins

Exposure to certain gases and heavy metals is a rare cause of encephalopathy, parkinsonism, and dystonia, probably as a result of cellular hypoxia from mitochondrial dysfunction or the generation of free radicals. *Carbon monoxide* toxicity appears to result from a combination of tissue hypoxia and direct cellular toxicity. After initial recovery, about 10 percent of survivors will develop parkinsonism several weeks to months later; approximately 80 percent recover within 6 months. Imaging often reveals focal injury particularly to the pallidum and diffuse white matter changes, and the findings on magnetic resonance spectroscopy of white matter lesions are consistent with demyelination. Treatment with levodopa and anticholinergic agents usually is unhelpful.

Parkinsonism and dystonia are common among survivors of *cyanide poisoning*. The movement abnormalities may initially improve, only to worsen days to months later, followed by stabilization and gradual but incomplete recovery. Cyanide reacts with cytochrome-*c* oxidase, causing cellular hypoxia. Imaging studies show lesions in the caudate and lentiform nuclei, precentral cortex, and cerebellum. Functional imaging shows reduced dopamine transporter uptake suggestive of nigral neuronal loss.

Ingestion of *methanol* results in the production of formaldehyde by the liver; the liver and erythrocytes synthesize formic acid, which inhibits cytochrome-*c* oxidase and, thus, mitochondrial electron transport and tissue adenosine triphosphate production. Metabolic acidosis injures the retina and optic nerves and leads to necrosis of the putamen, subcortical white matter, cerebellum, brainstem, and spinal cord, resulting in parkinsonism, dystonia, tremor, and blindness. Initial treatment relies on correction of the metabolic acidosis with ethanol and elimination of methanol with hemodialysis. Gradual improvement may occur with time, and treatment with amantadine and dopaminergic medications sometimes helps.

Manganese toxicity may occur as an occupational exposure (e.g., in miners of the ore or with chronic exposure to metal alloys, batteries, paint, varnish, enamel, or colored glass), or as a consequence of liver failure. Manganese increases free radical formation, inhibits antioxidant function, may reduce mitochondrial energy production, and perhaps increases glutamate neurotoxicity. In addition to foot dystonia, parkinsonism, early freezing of gait, a distinct gait disturbance (cock gait), hyperreflexia, and Babinski signs may occur. Remission may occur in mild cases if further exposure is prevented, but the course is otherwise progressive. There are reports of improvement after chelation. Pathologic examination reveals damage to the globus pallidus and substantia nigra pars reticulata (which are downstream from the nigrostriatal dopaminergic pathway), consistent with the failure to respond to levodopa. Magnetic resonance imaging (MRI) may show hyperintensity of the putamen on T1-weighted images. A similar syndrome (with elevated serum manganese and putamen T1 hyperintensity) has been described in methcathinone users when the drug was produced using potassium permanganate oxidation of ephedrine or pseudoephedrine.

Organic *mercury* poisoning, as seen formerly with the ingestion of certain fungicides and shellfish (Minamata disease), causes visual loss, ataxia, paresthesias, and cognitive dysfunction. Choreoathetosis, parkinsonism, and tremor also occur, and dystonic posturing is occasionally seen. Inorganic mercury poisoning, seen in glass blowers, hatters, and battery workers, produces a psychotic encephalopathy and tremor.

Dystonia secondary to copper accumulation occurs in *Wilson disease*. If hepatic damage is mild, significant improvement follows chelation therapy with penicillamine or trientine and zinc, which reduces dietary absorption of copper. Liver transplantation may be required for nonresponders and patients with severe liver dysfunction. The movement disorder may respond to trihexyphenidyl, levodopa, dopamine agonists, or amantadine.

Cellular and global hypoxia-ischemia have been implicated in *disulfiram* overdose. In one such case, psychomotor slowing and parkinsonism were evident several days after awakening from coma, and over 10 years progressed to include dystonia of a lower limb, the eyelids, and speech. Brain computed tomography (CT) shows hypodense lesions, and MRI shows hyperintense lesions in the pallidum and inferior putamen. Chorea has also been described as a consequence of toluene (glue sniffing) and thallium exposures.

Drug-Induced Dystonia and Chorea

Medications may cause dystonia (Chapter 32) and chorea (Table 58-1). Acute iatrogenic dystonic reactions are idiosyncratic, reversible, and common. They may occur almost immediately (minutes to hours) after the first dose of a medication, or days to weeks later. For dystonia, the most common offenders include antipsychotics (both typical and atypical), benzodiazepines, anticonvulsants, dopamine agonists, and tricyclic antidepressants.[4] Reactions have been encountered less often with calcium-channel blockers, propranolol, histamine-blocking drugs (cimetidine, ranitidine, cetirizine), and substituted benzamides (metoclopramide, sulpiride, clebopride, and domperidone). Patients with AIDS dementia complex are particularly sensitive to neuroleptic-related acute dystonic reactions because of underlying dopaminergic dysfunction. Dystonia may occur soon after starting antidepressants or develop after chronic use. Many agents (and medication classes) may be responsible including tetracyclics (trazodone and amoxipine), tricyclics (clomipramine, amitriptyline, and imipramine), selective serotonin reuptake inhibitors (including fluoxetine, paroxetine, fluvoxamine, escalopram, citalopram, and sertraline), and serotonin-norepinephine reuptake inhibitor (duloxetine).[4]

If dystonia develops acutely, treatment involves discontinuation of the offending agent and administration of an anticholinergic drug or benzodiazepine. Diphenhydramine, benztropine mesylate, chlorpheniramine, diazepam, or lorazepam may be given orally or intravenously; treatment for several days is sometimes necessary, especially if the causal agent was taken regularly or in depot form. If dystonia is mild or develops slowly, gradual down-titration of the medication is appropriate.

Chorea has been reported secondary to a variety of medications including anticonvulsants (phenytoin, carbamazepine, valproate, and gabapentin), stimulants (amphetamine, cocaine, methylphenidate, pemoline), benzodiazepines, estrogens, lithium, levodopa (with or without catechol-*O*-methyltransferase inhibitors), dopamine agonists, tricyclic antidepressants, and antihistamines, as well as other agents such as baclofen, cimetidine, thyroxine, cyclosporine, and aminophylline.[4] Chorea and encephalopathy has been associated with ciprofloxacin use and also with 4-aminopyridine overdose. Disulfiram overdose or poisoning (discussed

TABLE 58-1 ■ Selected Drugs and Toxins Inducing Chorea and Dystonia

Drug or Toxin	Chorea	Dystonia
Anticholinergics	Benzhexol, trihexyphenidyl	–
Antiepileptics	Carbamazepine, felbamate, gabapentin, lamotrigine, phenytoin, valproic acid	–
Anti-infectious agents	Ciprofloxacin	–
Antidepressants and anxiolytics	Tricyclic agents	Selective serotonin reuptake inhibitors, tricyclic agents, benzodiazepines
Cardiac medications	Flecainide	Flecainide
Calcium-channel blockers	–	Cinnarizine, flunarizine, verapamil
Dopamine agonists and levodopa	Apomorphine, bromocriptine, pergolide, pramipexole, ropinirole, lisuride, cabergoline, levodopa	Apomorphine, bromocriptine, pergolide, pramipexole, ropinirole, lisuride, cabergoline, levodopa
Dopamine-receptor blocking drugs	Antipsychotics, metoclopramide, antiemetics	Antipsychotics, metoclopramide, antiemetics
Histamine-receptor blocking drugs	Cyproheptadine	Cimetidine, ranitidine, cetirizine
Hormones	Oral contraceptives, estrogens, thyroxine	–
Immunosuppressants	Corticosteroids, cyclosporine	–
Stimulants	Amphetamine, cocaine, methylphenidate, pemoline	–
Serotonin receptor antagonists	Ondansetron	Ondansetron
Miscellaneous drugs	Baclofen, digoxin, lithium, theophylline, 4-aminopyridine	Clebopride, disulfiram, domperidone, metoclopramide, sulpiride
Toxins/metals	Mercury, organophosphates, thallium, toluene	Carbon monoxide, cyanide, disulfiram, manganese, methanol, mercury, thallium

earlier) may present clinically with encephalopathy, ketotic hyperglycemia, and dystonia.

Tardive syndromes develop after the introduction of the provoking medication, usually a dopamine receptor blocking drug. Most patients have been on the medication for at least 3 months; the disorder may first manifest after the causal agent has been discontinued, but typically does so within 6 months of withdrawal. The syndrome may involve dyskinesias, typically repetitive orolingual facial movements or repetitive movements of the head, trunk, and extremities. Older patients seem more susceptible than young persons. A tardive syndrome also may take the form of dystonia, chorea, akathisia, tremor, or myoclonus.

A number of medications have been associated with the development of tardive dyskinesia. It occurs most commonly with haloperidol or typical antipsychotics, but it is also common with the atypical antipsychotic drugs and with prolonged use (i.e., for more than 3 months) of metoclopramide. Other dopamine-blocking agents such as the antiemetics prochlorperazine and promethazine may cause tardive syndromes. Less commonly, certain calcium-channel blockers (especially cinnarizine and flunarizine) and rarely serotonin reuptake inhibitors have been associated with its development. The causal agent should be discontinued if feasible; otherwise, patients requiring antipsychotic medication should be switched to an atypical antipsychotic drug such as quetiapine. The withdrawal of dopamine-blocking agents may initially exacerbate the dyskinesia, but the movement disorder ultimately decreases or disappears in up to 50 percent of patients, persisting unchanged in the remainder. Dopamine-depleting agents (valbenazine, tetrabenazine, reserpine) are the most useful adjunctive treatments, followed by benzodiazepines such as clonazepam; GABA agonists such as baclofen and sodium valproate also have been used, but evidence of benefit is sparse. Anticholinergic drugs may exacerbate the syndrome.

Tardive dystonia may be indistinguishable from idiopathic dystonia and may respond to sensory tricks. It may be focal, segmental, or generalized; however, the head and neck region are most commonly affected, resulting in torticollis, blepharospasm, or oromandibular dystonia. Orobuccal-lingual dyskinesia or other tardive movements may occur in tardive dystonia, unlike in idiopathic dystonia. The onset is insidious, typically after several years of antipsychotic use, but may occur with exposures shorter than 1 year. Tapering the antipsychotic occasionally produces gradual or partial remission of tardive dystonia, often after an initial worsening. An increase in dose of the antipsychotic or its continuation may lead to temporary benefit, but probably worsens the long-term outlook. If treatment with an antipsychotic is necessary, replacement of the original neuroleptic with clozapine or quetiapine has been helpful. Approximately 50 percent of patients benefit from dopamine-depleting or -blocking agents and anticholinergic treatment. For patients with focal or segmental dystonia, botulinum toxin injections are beneficial. Stereotactic surgery, including pallidotomy and pallidal deep brain stimulation, has been successful for severe tardive dystonia unresponsive to other measures.

Some medications appear to cause chorea in the setting of pre-existing basal ganglia injury. For example, dose-related dyskinesias develop in a large proportion of parkinsonian patients taking carbidopa-levodopa. Similarly, many patients who develop chorea while taking oral contraceptives have had striatal abnormalities on imaging studies or have a past history of Sydenham chorea, chorea gravidarum, or chorea with Henoch–Schönlein purpura.

Among illicit drugs, cocaine and amphetamines have been most frequently associated with dyskinesias. Both influence central dopaminergic mechanisms, and cocaine also decreases serotonin turnover and degradation. Both may lead to choreoathetoid movements of the extremities, less often the head or trunk, or buccolingual dyskinesias within 24 hours of use; these typically resolve without treatment in 2 to 6 days. However, in chronic users, chorea persisting for more than 1 year after discontinuation of these stimulants has been described.

Infectious Disorders

Infections may cause the full spectrum of movement disorders (Table 58-2). Movement abnormalities usually develop during the acute illness and are transient, but abnormal movements sometimes begin or persist after the infection has cleared. One mechanism is vasculitic ischemia of the basal ganglia, although direct neuronal injury by the organism or a toxin, and autoimmune cross-reactivity with basal ganglia epitopes are also postulated to play a role.

BACTERIAL INFECTIONS

Sydenham chorea is a transient chorea that develops in about one-quarter of patients with rheumatic fever, an autoimmune complication of infection with group A β-hemolytic streptococci. It is the most common cause of acute chorea in children, typically affecting those between ages of 7 and 12 (with a range of 3 to 17) years. After 10 years of age, it is more common in girls. The chorea is usually generalized (80% of cases), and may be the presenting feature of rheumatic fever; cardiac involvement is present in the majority. An encephalopathy occurs in 10 percent. Dysarthria and behavioral abnormalities are common; obsessive-compulsive disorder and attention deficit and hyperactivity occur in about 25 percent of patients. The pathogenesis of Sydenham chorea may be related to the development of antineuronal antibodies. Although the condition usually improves over months, residual chorea has been observed in 50 percent of patients 2 years after onset, and behavioral abnormalities may persist. Symptomatic treatment with valproic acid, carbamazepine, or clonidine may be considered in those with troublesome chorea. Dopamine-receptor blocking drugs are reserved for those who do not respond to these other agents, and brief case reports suggest that tetrabenazine may also be helpful. In severe cases a brief course of prednisone has been prescribed to shorten the course of the disease, and there are also anecdotal reports of benefit from intravenous immunoglobulins (IVIg) or plasmapheresis. In about half of affected patients, chorea recurs within 2 years of the initial episode in the absence of infection. A course of penicillin is usually initiated at the time of diagnosis and continuous prophylaxis with penicillin is often advised to prevent further streptococcal infections until adulthood. Neuroimaging studies may be normal or show contralateral or bilateral striatal abnormalities that resolve as the chorea settles. Positron emission tomography (PET) scanning shows reversible striatal hypermetabolism.

Tuberculous meningitis may cause dystonia or chorea. Brain imaging may be normal or show ischemic or hemorrhagic infarcts. Direct infection or infarction of the basal ganglia may account for the development of the movement disorder. Treatment is with antituberculous therapy. Most patients improve over several weeks.

Mycoplasma pneumoniae causes pneumonia but also affects the CNS in approximately 5 percent of patients

TABLE 58-2 ■ Movement Disorders Produced by Various Infectious Agents

Infectious Agent	Chorea	Dystonia	Myoclonus	Tremor	Parkinsonism
Arboviruses	X				X
Cytomegalovirus	X	X		X	
Enteroviruses	X				X
Epstein–Barr virus	X				
Herpes simplex viruses	X				
Herpes zoster virus			X	X	X
HIV	X		X	X	X
HIV plus *Toxoplasma gondii*	X	X		X	X
HIV plus herpes zoster			X		
HIV plus *Mycobacterium tuberculosis*	X				
HIV plus *Treponema pallidum*	X				
Influenza viruses	X	X		X	
Japanese encephalitis virus	X	X		X	X
Lassa virus				X	
Machupo virus (Bolivian hemorrhagic fever)				X	
Measles virus	X		X		X
Paramyxovirus (mumps)	X		X		
Rubella virus	X			X	
African trypanosomiasis				X	X
Corynebacterium diphtheriae	X				
Lyme borreliosis			X		
Legionella species	X				
Mycoplasma pneumoniae	X	X			X
Salmonella species	X		X	X	X
Group A *Streptococcus*	X	X			X
Mycobacterium tuberculosis	X	X	X	X	X
Treponema pallidum	X				
Plasmodium falciparum	X	X	X	X	X
Schistosoma mansoni			X (segmental)		
Tropheryma whipplei			X	X	X
Taenia solium (neurocysticercosis)	X	X	X	X	X
Cryptococcal meningoencephalitis			X		X
Prions			X		X

Adapted from Alarcón F, Giménez-Roldán S: Systemic diseases that cause movement disorders. Parkinsonism Relat Disord 11:1, 2005.

requiring hospitalization. Aseptic meningitis, cranial neuritis, transverse myelitis, or encephalitis may occur, and neurologic symptoms may precede pulmonary ones. Generalized choreoathetosis and dystonia have been described. Cerebral imaging may be unremarkable or show abnormalities in the caudate, putamen, and globus pallidus. The cerebrospinal fluid (CSF) is normal or exhibits a mild lymphocytosis with elevated protein concentration. The diagnosis is made by respiratory cultures and tests for serum and CSF complement-fixing and cold agglutinin antibodies.

In Legionnaire disease (*Legionella pneumophila*), high fevers and pulmonary involvement may be accompanied in approximately 20 percent of cases by headache and, rarely, by chorea. The CSF and head CT scan are normal, and the diagnosis is made by serologic studies. The chorea may persist for up to 2 years.

Chorea has also been reported uncommonly in patients with Lyme encephalitis or neurosyphilis and rarely with other infections.

VIRAL INFECTIONS

Viral encephalitis (including Japanese encephalitis, West Nile, St. Louis, herpes simplex, dengue, mumps, and measles) may be accompanied by movement disorders. Japanese encephalitis, endemic to much of Asia, causes dystonia or parkinsonism several weeks after infection. Brain MRI typically shows abnormalities in the thalamus, globus pallidus, or putamen. Varicella has been associated with transient chorea and dystonia. Chorea can be an early feature of herpes simplex encephalitis but more frequently signals a relapse. In adults, human immunodeficiency virus (HIV) infection may present with hemichorea-hemiballism or with generalized chorea, usually in the presence of dementia. Most AIDS-related cases are secondary to toxoplasmosis but may also relate to HIV encephalitis, cryptococcal infection, or progressive multifocal leukoencephalopathy.

FUNGAL AND PARASITIC INFECTIONS

In HIV-seropositive patients, cerebral toxoplasmosis is the most common cause of dyskinesia. *Toxoplasma* abscesses in various diencephalic structures have been associated with contralateral limb ballism, choreoathetosis, and dystonia. Treatment of the infection is usually successful, but improvement in the dyskinesia is seen in only approximately 25 percent of instances, suggesting irreversible injury to the basal ganglia. Improvement of the dyskinesia may occur with dopamine-blocking agents or dopamine depleters such as tetrabenazine. Hemichorea and hemiballismus have been reported only rarely in cryptococcal meningitis and may respond to antifungal treatment.

Autoimmune, Inflammatory, and Paraneoplastic Disorders

In systemic lupus erythematosus (SLE), choreoathetosis develops in 1 to 2 percent of patients and may be the presenting feature.[5] Women are affected more commonly than men. The chorea typically occurs before the age of 30 years and tends to manifest during a lupus flare, often accompanied by behavioral disorders. It may be generalized or lateralized and is usually transient, lasting for a few days up to 3 years; recurrence occurs in approximately 25 percent of cases. Rarely, the chorea is permanent. The chorea may be self-limited or respond to corticosteroid or symptomatic treatment. Imaging studies may be abnormal, but the location of lesions does not usually explain the chorea.

Patients with SLE and chorea may possess antiphospholipid antibodies (lupus anticoagulant or anticardiolipin antibody) that predispose to endovascular thrombosis and cerebral infarction.[6] Approximately 30 percent of patients with SLE and these antibodies have thrombotic events. Laboratory studies reveal that whole-blood clotting time is prolonged, and the prothrombin time and the Russell viper venom time may be abnormal. Chorea in several patients with SLE and antiphospholipid antibodies has improved within days on aspirin therapy or warfarin, consistent with a vascular mechanism. Thus, chorea in SLE may result from autoimmune vasculopathy or direct antibody-mediated basal ganglia dysfunction, or both.[6]

The antiphospholipid syndrome may occur in the absence of SLE or other autoimmune conditions, the so-called primary antiphospholipid syndrome. Clinically and pathophysiologically, this condition is indistinguishable from that associated with SLE. In addition to lupus anticoagulant and an IgG anticardiolipin antibody, many patients have a low titer of antinuclear antibody, 30 percent have a false-positive Venereal Disease Research Laboratory test, and some have antithyroid antibodies. Chorea (either lateralized or generalized) has been the most frequently reported movement disorder, occurring in 1 to 4 percent of patients with primary or secondary antiphospholipid syndrome, although tics, dystonia, myoclonus, and corticobasal syndrome may occur. Brain MRI shows lesions of the basal ganglia in 6 to 16 percent of patients; labeled glucose PET imaging has revealed increased uptake contralateral to the hemichorea. For patients with no vascular events, treatment may consist of discontinuation of estrogen or progesterone (if applicable) and immunosuppressant treatment. For patients who have had a vascular event, anticoagulation may reduce the risk of recurrent thrombosis.

Chorea is a rare complication of polyarteritis nodosa and isolated angiitis of the CNS, and athetoid movements have been noted as the initial manifestation of primary Sjögren syndrome. Patients with Behçet syndrome (recurrent oral and genital ulcers, uveitis, and skin lesions) may present with chorea, jaw-opening dystonia, or paroxysmal dystonia. Typically, these patients have had an increased CSF protein concentration and lymphocytosis. They respond to immunosuppression but may require other agents to control abnormal movements. Chorea may also develop in Churg–Strauss syndrome.

Chorea sometimes occurs in Hashimoto encephalopathy. The CSF protein concentration is usually elevated, and some samples have oligoclonal bands or a mononuclear pleocytosis. Characteristically, the electroencephalogram (EEG) shows epileptiform activity, and transient or permanent areas of increased T2 signal are seen on brain MRI, particularly in the frontal and temporal lobes. Patients respond to prednisone, with a slow taper once improvement is stable. Complete remissions can be anticipated, although relapses sometimes occur or a deficit remains. Spontaneous remissions are rare.

Dystonia and tremor or chorea may be part of a movement disorder associated with celiac disease. Abdominal pain, ataxia, diarrhea, and myoclonus may also occur. Diagnosis is supported by demonstration of gliadin antibodies and characteristic findings on small bowel biopsy. The condition may respond to a gluten-free diet.

Chorea and dystonia are rare complications of paraneoplastic syndromes. In a series of 979 patients with paraneoplastic diseases, 9 presented with chorea and 3 had dystonia or dyskinesia.[7] Most had small-cell cancer of the lung, and one each had nonsmall cell lung cancer, renal cancer, and colon cancer. Most of these patients had CV2/collapsing response-mediator protein (CRMP)-5 antibodies, but ANNA-1 (anti-Hu) antibodies were found in four. In many patients, chorea was the initial symptom. CSF was abnormal in some patients. Brain imaging was abnormal in four of the nine patients, with diffuse hyperintensity of the white matter in T2-weighted MRI; two showed basal ganglia hyperintensity. Improvement may occur with cancer treatment or symptomatic medications (dopamine-blocking or -depleting medications or benzodiazepines). Laryngospasm, jaw-opening dystonia, and cervical dystonia have been described in paraneoplastic syndromes associated with antineuronal nuclear antibody type 2 (ANNA-2, also known as anti-Ri antibodies, associated most commonly with breast or lung cancer).[8]

Patients with anti–*N*-methyl-D-aspartate receptor encephalitis are usually women and many have ovarian cancers; various other cancers have also been reported. Patients commonly present with behavioral changes and seizures, and have dyskinesias (chorea, dystonia) involving the face, trunk, abdomen, and extremities in 80 percent of cases; orobuccolingual dyskinesias are most common. The dyskinesias usually respond to tetrabenazine, deutetrabenazine, or valbenazine.

Metabolic Disorders

The association between thyrotoxicosis and choreoathetosis or dystonic posturing was recognized by Gowers in 1893, particularly in young women, but patients of either sex may be affected. Chorea occurs in about 1 to 2 percent of those with *hyperthyroidism* and its course usually parallels that of the thyroid disorder. Abnormal movements typically involve the limbs, sometimes unilaterally, and are most conspicuous distally; the neck and face may also be affected. Paroxysmal (rather than more continuous) choreoathetosis may occur in rare instances; paroxysmal and kinesigenic choreoathetosis have also been reported with iatrogenic hyperthyroidism. No cerebral lesions have been noted on MRI or at autopsy. Treatment consists primarily in normalization of thyroid function (antithyroid drugs, radioiodine, or thyroidectomy). Chorea may respond to dopamine receptor blockers or propranolol even before hyperthyroidism has resolved. Altered dopamine turnover or increased dopamine receptor sensitivity may be responsible for the dyskinesia. Since chorea may occur in both hyperthyroidism secondary to Graves disease and iatrogenic thyrotoxicosis, it is hypothesized that the disorder results from a direct effect of thyroxine on the basal ganglia, perhaps by increasing dopamine receptor sensitivity.

Hypocalcemia from idiopathic hypoparathyroidism rarely may cause dystonia or choreoathetosis.[9] The abnormal movements may be the presenting complaint, may be asymmetric, are usually paroxysmal, and rarely are kinesigenic. Patients are usually younger than 30 years, with calcium levels of 4 to 6 mg/dL, elevated serum phosphorus levels (5 to 12 mg/dL), and low serum magnesium. Brain imaging frequently reveals basal ganglia calcification that persists after treatment of hypocalcemia and resolution of chorea or dystonia.

Generalized chorea or hemiballism-hemichorea may occur in *nonketotic hyperosmolar hyperglycemia*. Brain CT may show high-density lesions, and MRI often shows high T1 signal and hypoperfusion in the caudate or putamen contralateral to the side involved clinically. These imaging findings are considered to be a consequence of hyperviscosity and cytotoxic edema, not petechial hemorrhage. The chorea may resolve with correction of hyperglycemia; however, dopamine-depleting or -blocking agents may be useful treatments until the condition resolves. Severe *hypoglycemia* may be accompanied by either generalized chorea or hemichorea that resolves as blood glucose normalizes.

Dystonia or chorea has rarely been noted in hypernatremic dehydration, hyponatremia, and hypomagnesemia and also after central pontine myelinolysis. In addition, many inherited metabolic disorders or inborn errors of metabolism can cause chorea or dystonia, as is reviewed elsewhere.[10]

Other Causes

Post-traumatic focal and hemidystonia may occur rarely as a long-term consequence of severe head injury or following peripheral injury. Chorea-ballism may also follow head injury, as may functional movement disorders.

Approach to Diagnosis

The evaluation of patients with involuntary movements or postures requires a detailed history, as outlined earlier. Characterization of the movement disorder and its distribution, together with findings such as organomegaly, skin lesions, retinal or optic nerve disease, or neurologic deficits, narrows the differential diagnosis. The relaxed patient must be observed carefully while lying, sitting, standing, and walking to determine whether any abnormality is exacerbated by movement or rest. The patient should perform tasks that are particularly impaired because certain movement disorders are solely task specific.

The age of onset and the pattern of involvement and progression vary with the etiology. Focal or task-specific dystonias, often associated with a dystonic or essential-type tremor, onset in adulthood, a benign history, and no other abnormalities on examination are usually idiopathic. Limb dystonia beginning as action dystonia is usually idiopathic, whereas dystonia beginning at rest is sometimes symptomatic. Dystonia with onset in the legs is usually idiopathic in children but symptomatic in adults. Chorea or dystonia of acute or subacute onset or having a rapidly progressive course is more likely to be symptomatic. Hemidystonia at any age suggests a secondary etiology, and approximately 75 percent of patients have contralateral basal ganglia abnormalities on imaging, a history of hemiparesis, or both. One-third of hemidystonic patients have infarction or hemorrhage of the contralateral basal ganglia, especially the putamen. Generalized dystonia beginning at an early age may be idiopathic or symptomatic, but it is more often symptomatic when onset is in adulthood. Childhood-onset dystonias tend to become generalized, whereas those commencing in adulthood often remain focal or segmental. Similarly, tardive dystonia may be generalized in children, but it usually remains focal or multifocal in adults. Thus, dystonia of sudden onset, rapid progression, onset in infancy, cranial onset in children, lower-extremity onset in adults, or hemidystonia at any age is more likely symptomatic and requires full evaluation.

A large number of factors contribute to decision-making in the evaluation of chorea and dystonia. Brain MRI has a high yield, and basic laboratory studies include a complete blood count and blood electrolytes, calcium, phosphorus, uric acid, and liver and thyroid function tests. Any patient with chorea or dystonia younger than 40 years must be evaluated for Wilson disease. Evaluation for vascular disease, a hypercoagulable state, connective tissue disorders, and antiphospholipid antibodies may be required. Serum antistreptolysin O or antihyaluronidase titers and an electrocardiogram are useful when Sydenham chorea is suspected. Neurodegenerative and hereditary metabolic disorders require a separate battery of studies, which are described elsewhere.

Treatment

The treatment of secondary dystonia or chorea is difficult. In symptomatic cases, the underlying pathologic process should be treated first, as discussed earlier. General therapeutic measures may provide symptomatic benefit when specific treatments of the underlying lesion have failed to temper the movement disorder satisfactorily. Anticholinergics, dopaminergics, antidopaminergics, benzodiazepines, anticonvulsants, and certain other medications (discussed later) are used, based on patient age, tolerance, co-existing medical illnesses, and interactions with other medications taken concomitantly. All of these medications are disappointingly variable in their efficacy. Unfortunately, there is a paucity of adequate trials demonstrating therapeutic benefit or comparative efficacy because patient numbers are small, common side effects make double-blinding difficult, and nonspecific effects such as sedation can diminish abnormal movements. Moreover, spontaneous remissions, partial or complete, and transient or permanent, may occur unpredictably.

Anticholinergic medication, of which trihexyphenidyl is the best studied, is more effective in mild dystonia and in younger patients. Approximately one-third of patients with secondary dystonia benefit, and up to 50 percent of those with perinatal hypoxic injury improve. The selected agent is started at a low dose, which is increased slowly, depending on response and tolerance. (A particular daily dose may take several weeks to produce maximal benefit.) Side effects can be dose-limiting, particularly with advancing age. Tricyclic antidepressants and diphenhydramine are also sometimes used for their anticholinergic effects.

The useful antidopaminergic medications include dopamine depleters (reserpine, tetrabenazine, deutetrabenazine, valbenazine) or dopamine receptor antagonists. Valbenazine is particularly helpful for tardive dyskinesia.

Dopaminergic supplementation using levodopa is singularly effective in patients with dopamine-responsive dystonia, which may be present in 5 to 10 percent of patients with childhood-onset hereditary dystonia beginning in the legs, with or without diurnal fluctuations. It is less useful in treating symptomatic dystonias. In some instances, levodopa actually worsens symptomatic dystonia, whereas improvement may occur with dopamine agonists or amantadine.

Anticonvulsants have been tried and sometimes help, but usually the results are disappointing. Baclofen, a presynaptic γ-aminobutyric acid agonist, is also frequently tried and occasionally is effective, either orally or intrathecally. Other medications that have been tried alone or in combination, with variable benefit, include benzodiazepines, particularly clonazepam (which helps perhaps one-quarter of patients with secondary dystonia), muscle relaxants, cyproheptadine, and lithium. Adult-onset cranial or focal limb dystonias are best treated with intramuscular botulinum toxin.

Surgical approaches are sometimes warranted. Deep brain stimulation of the globus pallidus is effective for primary dystonia, myoclonus dystonia, and tardive dystonia. Selective peripheral denervation is sometimes successful for blepharospasm and cervical dystonia, but is now generally reserved for cases refractory to botulinum toxin. The use of deep brain stimulation for refractory chorea is being explored.

MYOCLONUS

Myoclonus is an acute, brief, involuntary jerk caused by a sudden muscle contraction (positive myoclonus) or relaxation (negative myoclonus). It can be classified by distribution, the location of the generator, or the underlying etiology. It may recur in the same muscle groups (focal or segmental myoclonus) or asynchronously and asymmetrically in different muscle groups (multifocal or generalized myoclonus), and it may occur at rest (spontaneous), on movement (action or intentional myoclonus), or in response to specific stimuli (reflex myoclonus).

Myoclonus occurs in healthy individuals (hiccups, hypnic jerks) or as a movement disorder with an idiopathic (essential), epileptic, or symptomatic etiology. Symptomatic myoclonus is the most common variety and may be due to primary neurologic causes, but it is more commonly seen in a general medical setting, to which this section is devoted. Myoclonus may be generated from spinal, subcortical, or cortical circuits and involves the somatotopically organized dorsal column/lemniscal and corticospinal systems superimposed on the spinoreticular and reticulospinal circuits.

Hypoxia-Ischemia

STROKE

Strokes involving the thalamus or brainstem may cause focal or segmental myoclonus that sometimes responds to levetiracetam, clonazepam, valproate, zonisamide, or primidone. Local injection of botulinum toxin may also be worthwhile.

GLOBAL HYPOXIA-ISCHEMIA

Posthypoxic action myoclonus may occur in survivors of cardiopulmonary arrest. Two forms of myoclonus are recognized in this context.

Acute posthypoxic myoclonus is characterized by severe, generalized myoclonus in comatose patients. The jerk-like movements develop within the first day after hypoxia and are characterized by violent flexion movements. If myoclonus persists for more than 30 minutes or for most of the resuscitation day, it is often called myoclonus status epilepticus, despite the lack of evidence that the myoclonus is epileptic in nature. In most patients with posthypoxic myoclonus, an EEG performed on the first hospital day demonstrates a burst-suppression pattern, alpha-pattern coma, or polyspike-wave activity. Myoclonus status epilepticus occurs in 30 to 40 percent of comatose adult survivors of cardiopulmonary resuscitation, is difficult to control, and has a poor prognosis. Approximately 90 percent of patients with myoclonus status epilepticus have a fatal outcome, a few survive but in a persistent vegetative state, and only 2 to 3 percent survive with a good outcome.

Chronic posthypoxic myoclonus (Lance–Adams syndrome) occurs within days to weeks after hypoxic injury, often while the patient is still comatose or is beginning to recover consciousness. The myoclonus predominantly involves the limbs and is precipitated by active or passive movement; it occasionally spreads to other portions of the body. It may be stimulus sensitive, and negative myoclonus may also occur, predisposing patients to falls. Cerebellar ataxia and cognitive impairment are often associated. Treatment of chronic posthypoxic myoclonus is not satisfactory. However, levetiracetam, clonazepam, valproate, zonisamide, and piracetam (not available in the United States) are often helpful. Treatment with 5-hydroxytryptophan (often with carbidopa to limit nausea) or with sodium oxybate may also be worthwhile, based on anecdotal reports or pilot studies.

Metabolic Disorders

Metabolic disorders are commonly associated with mental status changes and negative myoclonus (asterixis), which is usually of brainstem reticular origin. Renal failure and its treatment may both be associated with neurologic dysfunction. Generalized and multifocal positive and negative myoclonus occur in *uremic encephalopathy* (Chapter 16). It may occur at rest, with movement, or in response to a stimulus. Myoclonus also occurs in patients with *dialysis dementia* (Chapter 16). The myoclonus is exacerbated during and after dialysis and is most prominent in the face and upper limbs.

In *hepatic insufficiency* of any cause, asterixis is typical, but multifocal positive myoclonus also occurs. Treatment requires addressing the underlying disorder. In rare instances, Wilson disease may present with progressive myoclonus.

Hyperglycemia is the most common metabolic disturbance causing focal motor phenomena. In nonketotic hyperglycemia, severe hyperglycemia, hyperosmolality, and dehydration are accompanied by segmental or generalized myoclonic seizures in up to 20 percent of patients. Asterixis or negative myoclonus is also seen. EEG shows diffuse slowing, sometimes with a spike-wave pattern. The glucose level is typically over 600 mg/dL and osmolality above 300 mOsm/kg H_2O, with mild or absent ketoacidosis. Treatment is by fluid and electrolyte replacement and correction of hyperglycemia. The myoclonus resolves with treatment of the hyperosmolality, and not with anticonvulsants.

Vitamin B_{12} deficiency may cause myoclonus in children and adults. The myoclonus resolves after treatment with vitamin B_{12}. Myoclonus may also occur after intramuscular vitamin B_{12} administration.

Pellagra (niacin deficiency) is characterized by the triad of myoclonus, altered mental status, and generalized hypertonicity; a dermatitis is sometimes present. It typically occurs in alcoholism but can be seen in malabsorption conditions and after treatment with certain medications (5-fluorouracil, isoniazid, pyrazinamide, ethionamide, 6-mercaptopurine, hydantoins, phenobarbital, and chloramphenicol). Early replacement of niacin is required. Hypernatremic dehydration has also been associated with transient myoclonus and chorea in chronic alcoholism.

Finally, myoclonus may occur in a number of inborn errors of metabolism, as is reviewed elsewhere.[10]

Autoimmune and Inflammatory Disorders

Myoclonus occurs in about 40 percent of patients with *Hashimoto encephalopathy* (also called encephalopathy associated with autoimmune thyroid disease). Any combination of cognitive impairment, encephalopathy, psychosis, transient neurologic deficits, myoclonus or tremor, seizures, somnolence, or coma develops and fluctuates over weeks to months. The myoclonus may be generalized or multifocal and spontaneous or reflex-evoked, and is without EEG correlates. Patients are clinically euthyroid, with elevated antithyroid antibodies, the levels of which correlate poorly with the clinical state. Further clinical and laboratory details are provided in Chapter 18.

Myoclonus has been described in the *antiphospholipid syndrome*. Nonvasculitic *autoimmune inflammatory meningoencephalitis* may present with the rapid onset of dementia, parkinsonism, and myoclonus. In rare instances, the EEG shows persistent periodic sharp waves suggestive of Creutzfeldt–Jakob disease; dramatic clinical improvement has occurred with corticosteroids.

A myoclonic syndrome often accompanied by ataxia may occur in *celiac disease*, despite normal vitamin B_{12} and E levels. Typically, patients have a gastrointestinal syndrome that may include chronic diarrhea and abdominal pain, although gastrointestinal complaints may be subtle (only nausea and vomiting episodes during infection in one report). Action or reflex myoclonus may occur in patients with established celiac disease, but whether this relates to inadequate dietary restriction or poor compliance is uncertain. The myoclonus initially may be focal but usually becomes multifocal; generalized convulsions may develop. The jerks are usually preceded by a time-locked polyspike EEG discharge, supporting a cortical origin. In some cases improvement occurs after a gluten-free diet is instituted. Anticonvulsant or benzodiazepine therapy is commonly required but is incompletely effective. Opsoclonus-myoclonus has also been described in a child with celiac disease and responded to a gluten-free diet.

Drug- and Toxin-Induced Myoclonus

Neuroleptic malignant syndrome may complicate neuroleptic treatment but also occurs with dopamine-depleting agents and on withdrawal of dopaminergic treatments.

It is primarily due to functional dopamine deficiency, which leads to disinhibition of cortical and subcortical excitatory pathways; norepinephrine and serotonin may also be involved. Its incidence is 0.2 percent of patients exposed to neuroleptic agents. The disorder occurs within a month of starting the neuroleptic agent. Fever, rigidity, and an elevated serum creatine kinase (the major criteria) and tachycardia, labile blood pressure, tachypnea, diaphoresis (autonomic instability), altered mental status, and leukocytosis (the minor criteria) develop over 24 to 72 hours. Altered mental status and rigidity are often the first signs and are each present in over 95 percent of instances. The presence of all three major or two major and four minor criteria is highly predictive of the syndrome. The movement disorder is primarily an axial rigidity with tremor, choreoathetosis, dystonia, or myoclonus in the limbs. Rhabdomyolysis, renal insufficiency, respiratory failure, adult respiratory distress syndrome, disseminated intravascular coagulation, myocardial infarction, pulmonary embolism, and coma may complicate the picture.

The patient is best managed in the intensive care unit. Treatment involves discontinuing the offending neuroleptic or other precipitating drug (or reinstituting dopaminergic medication) and supportive therapy, including rehydration and reduction of body temperature by antipyretics or with artificial cooling if warranted. It may require administering the muscle excitation–contraction uncoupler dantrolene sodium at 1 to 2.5 mg/kg intravenously four times daily (maximum 10 mg/kg per day) and the dopamine agonist bromocriptine at 2.5 mg orally or via nasogastric tube four times daily (titrated up to 45 mg/day as required). Other dopamine agonists, amantadine, or carbidopa-levodopa can also be used in place of bromocriptine. Dopaminergic treatment should continue for 7 to 10 days, which is the usual duration of the disorder, and then slowly tapered. Rhabdomyolysis and renal failure are the greatest predictors of poor outcome. The mortality rate is between 10 and 20 percent. Survivors almost always achieve complete recovery.

The *serotonin syndrome* is a potential complication of treatment with antidepressants and related medications that increase cerebral serotonin neurotransmission. It is characterized by mental status changes, autonomic hyperactivity and neuromuscular abnormalities. The prerequisite is a recent increase in the dosage of a serotonergic agent or the addition of a new one. Cognitive and behavioral changes include confusion, hypomania, and agitation; myoclonus, ataxia, hyperreflexia, or tremor may also be present. Autonomic disturbances include nausea, vomiting, diarrhea, labile blood pressure, fever, shivering, and diaphoresis. Seizures may occur. The symptoms may begin as early as 2 hours after the medication is taken and usually resolve within 24 hours on discontinuation of the offending agent. When severe, serotonin syndrome may be indistinguishable from neuroleptic malignant syndrome and has a similar risk of multiple organ failure and death. Treatment requires discontinuation of precipitating drugs, supportive care, treatment for agitation with benzodiazepines and for hyperthermia with cooling measures and—if necessary—neuromuscular paralysis. Despite these measures, administration of a 5-HT$_{2A}$ antagonist such as cyproheptadine (4 to 8 mg, followed by 4 mg six times daily to a total of 0.5 mg/kg daily) may be necessary. Chlorpromazine (50 to 100 mg intramuscularly) has also been used for this purpose, but evidence of efficacy is lacking.

Of the non-neuroleptic psychiatric medications capable of causing myoclonus, *lithium* toxicity is well described. A variety of presentations occur including action, spontaneous, or stimulus-sensitive myoclonus, sometimes with opsoclonus. The myoclonus is of cortical origin but is not associated with epileptiform EEG abnormalities. Vomiting and a decreased level of consciousness may also be present; in rare instances the presence of cognitive changes and characteristic EEG findings suggests the erroneous diagnosis of Creutzfeldt–Jakob disease. Full recovery is usual. Overdose with *tricyclic antidepressants* may result in myoclonus because of their ability to inhibit reuptake of serotonin and norepinephrine. Myoclonus may occur with *levodopa* treatment. Reducing the levodopa dosage may diminish the myoclonus.

Tardive myoclonus due to neuroleptic medications is the least common of the tardive syndromes. It usually affects the face, neck, or upper limbs and responds to withdrawal of the neuroleptic treatment, but the movements may take several months to resolve. Benzodiazepines are sometimes useful.

A number of other medications and toxins have occasionally been associated with myoclonus and are summarized in Table 58-3. A pharmocovigilance study in 423 patients found drug-induced myoclonus was associated with anti-infectious agents (15%), antidepressants (15%), anxiolytics (14%), opiate agents (12%), antiparkinsonian medications (7%), and neurolepics (12%).[11]

Among illicit drugs, *cocaine* most commonly causes movement disorders. Myoclonus can be seen in the setting of a cocaine-induced disorder resembling neuroleptic malignant syndrome or as multifocal rest and action myoclonus together with opsoclonus and ataxia.

Myoclonus may develop in *gasoline sniffers* as a result of lead toxicity; it may be segmental or generalized and occurs spontaneously, with movement, or in response

TABLE 58-3 ■ Selected Drugs and Toxins Inducing Myoclonus

Anesthetics

Etomidate, enflurane, chloralose, methohexital, propofol, thiopental, spinal anesthesia

Anticonvulsants

Carbamazepine, gabapentin, phenytoin, lamotrigine, primidone, topiramate, valproic acid, vigabatrin

Antihistamines

Promethazine, omeprazole, oxatomide

Anti-infectious Agents

Carbenicillin, cephalosporins, ciprofloxacin, cefmetazole, gatifloxacin, imipenem, isoniazid, pefloxacin, piperazine, penicillin, (quinolones), ticarcillin, trimethoprim-sulfamethoxazole

Cardiac Medications

Diltiazem, flecainide, propafenone

Chemotherapeutic Agents

Busulfan, chlorambucil, ifosfamide, prednimustine

Dopaminergic Agents

Levodopa, dopamine agonists

Miscellaneous Medications

Amantadine, carisoprodol, cimetidine, metoclopramide, opiates, physostigmine, L-tryptophan

Narcotics

Diamorphine, fentanyl, hydrocodone, hydromorphone, methadone, meperidine, morphine, tramadol

Nonsteroidal Anti-inflammatory Drugs

Diclofenac

Psychiatric Medications

Antipsychotic medications, tricyclic antidepressants, lithium, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, clozapine, buspirone, lorazepam, methaqualone, midazolam, mirtazapine, sedative-hypnotics

Solvents and Gases

Acetone, carbon disulfide, ethyl benzene, methanol, ethylene oxide, formaldehyde, hydrogen sulfide, nitrous oxide, methyl chloride, methyl ethyl ketone, toluene

Heavy Metals

Aluminum, arsenic, bismuth salts, lead, manganese, organic mercury, thallium

Illicit Drugs

Cocaine, marijuana, methaqualone (Quaalude), methylenedioxymethamphetamine

Miscellaneous Agents and Toxins

Carbon monoxide poisoning, dichloroethane (used in dry cleaning), intrathecal water-soluble contrast media, tetraethyl lead

Pesticides

Aldrin, chlordane, chlordecone, cyclodienes, DDT, lindane, methyl bromide, organophosphate compounds, pyrethroids

Withdrawal Syndromes

Benzodiazepines, carbamazepine, dopaminergics

to an external stimulus. The condition may respond to chelation treatment with dimercaprol and calcium disodium edetate, although repeated exposures may result in a permanent encephalopathy. High serum levels of *bismuth*, used for treatment of certain gastrointestinal symptoms, may result in confusion followed by severe myoclonus, truncal ataxia, dysarthria, tremor, and sometimes generalized convulsions and coma. The syndrome can evolve slowly over months or acutely over days and has sometimes been confused with Creutzfeldt–Jakob disease or rapid-onset Alzheimer disease. The myoclonus may be multifocal or a massive generalized movement, and may occur spontaneously, on action, and in response to stimuli. Recovery over 3 to 12 weeks is the rule when the bismuth intake is discontinued early; chelation with dimercaprol may enhance renal clearance but has been associated with clinical deterioration in one patient. Diazepam, clonazepam, or valproic acid may reduce myoclonus.

Paraneoplastic Disorders

Multifocal myoclonus with opsoclonus is most commonly seen as a paraneoplastic syndrome. In children, 50 percent have an underlying neuroblastoma, whereas in adults it is more frequently associated with breast, ovarian, or small cell lung cancers. The most common antibody associated with paraneoplastic myoclonus is anti-Ri (ANNA-2) but myoclonus has also been associated with anti-Ma2, anti-Hu, and antiamphiphysin antibodies. PET with CT may be useful if initial radiologic screening is negative and early detection and treatment of the tumor appears to be useful. Occasionally the myoclonus improves with treatment of the underlying malignancy or prednisone, rarely with plasmapheresis, IVIg, cyclophosphamide, or immunoadsorption therapy with a protein A column. Myoclonus may respond to antiepileptic drugs.

Action and postural myoclonus has been reported in the setting of carcinomatous meningitis. It has also been described in a child with a rare cerebellar ganglioglioma, resolving with successful removal of the tumor.

Infections

Viral encephalopathies are the most common infectious cause of myoclonus (Table 58-2). In subacute sclerosing panencephalitis, myoclonus is time-locked to generalized bursts of high-voltage slow waves (periodic complexes) occurring approximately every 5 to 15 seconds on EEG. The myoclonus is relatively resistant to treatment, but sodium valproate, phenobarbital, carbamazepine, clonazepam, or levetiracetam may be tried. Herpes simplex virus encephalitis and postviral acute demyelinating encephalomyelopathy may also cause myoclonus. Segmental spinal myoclonus has occurred as a late complication of herpes myelitis.

Myoclonus occurs rarely with HIV infection. In a study of 2,460 inpatients with HIV infection, only 4 had myoclonus (2 with spinal myoclonus and 2 with generalized myoclonus).[12] Evaluation suggested four different causes: toxoplasmosis, HIV encephalopathy, tuberculous radiculomyelopathy, and herpes zoster. The myoclonus tends to be most prominent in the face, trunk, and proximal limbs and may be spontaneous or stimulated. Rarely, the myoclonus occurs with seroconversion, but usually the affected patients are significantly ill, often taking multiple medications. Treatment depends on the underlying cause; in some cases, myoclonus has resolved with antimicrobial treatment for opportunistic infections, retroviral therapy, or additional symptomatic medications. Other rare viral causes of myoclonus include mumps, chickenpox, parainfluenza virus type 3, coxsackievirus B3, poliovirus, St. Louis encephalitis, JC virus causing progressive multifocal leukoencephalitis, and encephalitis lethargica. Myoclonus or opsoclonus-myoclonus may also be the presenting symptom of West Nile virus infection.

Bacterial infections associated with myoclonus are less common than viral infections. Spinal myoclonus and opsoclonus-myoclonus have been reported in Lyme neuroborreliosis and in typhoid (enteric fever). Opsoclonus-myoclonus has also been described as a sequela of group A β-hemolytic streptococcal infection and responds to corticosteroid treatment. Multifocal myoclonus may be a rare feature of tuberculous meningitis or cerebral tuberculomas. Approximately 25 percent of patients with Whipple disease (discussed in Chapter 13) due to the gram-positive bacillus *Tropheryma whipplei* have myoclonus, although oculofacial and oculomasticatory myorrhythmias are the most characteristic movement disorders described.

Multifocal myoclonus may occur in the postmalaria neurologic syndrome, which also includes encephalopathy, tremor, and ataxia, beginning days to weeks after treatment of malaria. It responds rapidly to corticosteroids. Multifocal and oculopalatal myoclonus have also been reported in neurocysticercosis.

Injury by Physical Agents

Spinal myoclonus may develop as a late complication of spine irradiation for cancer. The high-pressure neurologic syndrome, which occurs on diving beyond a depth of 100 meters, consists of cognitive impairment and hyperkinesis. Myoclonus occurs at a depth of 300 to 500 meters or 50 to 60 atmospheres. Segmental myoclonus has been reported in the setting of electrical injury. Finally, myoclonus may occur as a long-term consequence of severe head injury.

Approach to Diagnosis

As mentioned earlier, the clinical approach to evaluation of myoclonus requires a detailed history and full neurologic and general medical examination. If the myoclonus is considered pathologic and no offending drug or toxin is appreciated, screening blood studies may include a complete blood count and erythrocyte sedimentation rate; determination of electrolyte and glucose levels; thyroid, renal, and hepatic function tests; and drug and toxin testing. An EEG to exclude an epileptic basis and brain and spine MRI to exclude structural causes are important. Paraneoplastic antibody testing may also be helpful.

Treatment

When possible, myoclonus should be treated by addressing the underlying medical disorder. Immunotherapy may help when postinfectious or paraneoplastic causes are responsible. The location of the generator of the myoclonus can guide treatment. Cortical myoclonus responds best to anticonvulsants, particularly sodium valproate (0.6 to 3 g daily), clonazepam (0.5 to 12 mg daily), levetiracetam (1,000 to 3,000 mg daily), primidone (50 to 1,000 mg daily), and piracetam (2 to 20 g daily). Reticular reflex myoclonus and spinal myoclonus may respond to clonazepam. Other medications that have been anecdotally useful include anticholinergic agents, baclofen, tetrabenazine, acetazolamide, and opiates; γ-aminobutyric acid receptor agonists may also be effective. Combinations of two or three medications may be more effective than monotherapy.

TREMOR

Tremor is the most common of all involuntary movements and is defined as an involuntary, rhythmic oscillation of a body part. It can be physiologic (normal) or pathologic, and is characterized by its frequency, amplitude, and distribution, and the position in which it occurs. Tremor is most easily classified as rest or action tremor.

Some forms of tremor are generated primarily by a central oscillator, as in essential tremor, and others, such as physiologic tremor, are mainly mechanical in origin. Central tremor is generated in the cerebellothalamocortical and dentatorubro-olivary pathways, with a poorly understood contribution from basal ganglia circuits. Rest tremor is characteristic of *parkinsonism*, which itself may occur secondary to a variety of causes. Such rest tremor is often accompanied by rigidity, bradykinesia, or postural instability, but may occur in isolation. Mechanical tremors decrease in amplitude and frequency with a load, whereas centrally generated tremors decrease only in amplitude.

Stroke

Tremor may occur as a consequence of stroke. The most common lesions involve the thalamus, mesencephalon, rubro-olivary tract, and cerebellar tracts. Limb tremor may occur with lesions of the cerebral cortex. Poststroke tremor is often unilateral or segmental rather than generalized, and may be associated with other movement disorders. It is usually an action tremor (i.e., postural or kinetic, or both). It often fails to respond to primidone or propranolol or to other symptomatic agents such as clonazepam, valproate, or anticholinergic agents, and, in severe cases, may necessitate thalamic deep brain stimulation.

Medications

It may be difficult to determine whether a tremor has been caused or simply enhanced by a particular medication.[13] Tremor is common and may be a normal finding (physiologic tremor). Other causes must be excluded before a tremor can be ascribed to medication. The timing of tremor onset in relation to the introduction of a medication or to dose adjustments may be suggestive, as may the symmetry of the tremor and its failure to progress other than with dose adjustments. Patients often take more than one medication, so that identification of the offending drug may be difficult. Drug interactions may confound recognition. Medications can cause the full spectrum of tremor subtypes (rest, postural, or kinetic), although postural tremor is most common (Table 58-4). Intention tremor refers to the subtype of kinetic tremor that becomes more prominent as the limb approaches the target. Most medication-induced tremors respond to dose reductions or discontinuation of the responsible agent.

Commonly used medications such as adrenergic agonists, including all β-agonists, lithium, caffeine, corticosteroids, tricyclic antidepressants, cyclosporine, and thyroid excess usually cause postural tremor. Dopaminergic and anticonvulsant medications also cause an enhanced physiologic tremor. Lithium- or valproate-induced tremor may be present at rest and is enhanced with posture or action.

Tremor is particularly common with lithium, valproate, and amiodarone. Lithium-related tremor occurs most often in the elderly, mainly affects the hands, and is usually mild. It may be enhanced by concomitant treatment with tricyclic antidepressants or selective serotonin reuptake inhibitors and alleviated by propranolol. The tremor induced by valproate is dose related and is more marked with immediate-release than controlled-release preparations. It may be ameliorated by propranolol, acetazolamide, or amantadine. The antiarrhythmic amiodarone may cause a postural and terminal movement tremor in up to 20 to 30 percent of patients. The tremor is dose dependent, may become apparent at any time during treatment, and usually improves or settles within weeks of dose adjustment or discontinuation of the medication. The mechanisms by which tremors are induced by these medications are unknown.[13]

Central monoaminergic stimulation by neuroleptics, phenylethylamines, and indoles may result in a parkinsonian rest tremor and a postural tremor. Specifically, tremor is seen in neuroleptic malignant syndrome and serotonin syndrome (discussed earlier). Dopamine receptor-blocking drugs and dopamine-depleting agents such as tetrabenazine and reserpine may also trigger a rest tremor.

Toxins and Recreational Agents

A variety of toxins cause tremor directly or as part of a withdrawal syndrome (Table 58-4). Tremor may occur with acute cocaine intoxication, and persists in abstinent cocaine-, alcohol-, and opiate-dependent subjects for months after the last use; rest tremor is reportedly more common in those with prior cocaine use. Alcohol and other drug withdrawal states enhance, sometimes asymmetrically, postural physiologic tremor, which decreases with time but can be treated with propranolol or benzodiazepines. The intention tremor of chronic alcohol abuse, however, is the result of cerebellar injury by alcohol. With cannabis use, withdrawal symptoms may occur after as little as 7 days of use and include tremor, irritability, restlessness, anorexia, fever, and other sympathetic effects.

Intoxication with heavy metals and organic compounds may produce a rest or action tremor, and

TABLE 58-4 ■ Drugs and Toxins Causing Tremor

Drug or Toxin	Kinetic or Postural Tremor	Intention Tremor	Rest Tremor
Anticonvulsants	Carbamazepine, felbamate, lamotrigine, phenytoin, tiagabine, topiramate, valproate, vigabatrin	—	Valproate
Antidepressants and mood stabilizers	Amitriptyline, lithium, MAOIs, SSRIs, valproate	Lithium	Lithium, SSRIs, valproate
Anti-infectious agents	Trimethoprim-sulfamethoxazole	Vidarabine	Trimethoprim-sulfamethoxazole, amphotericin
β-Adrenergic agonists	Salbutamol, salmeterol	Salbutamol, salmeterol	
Cardiac medications	Amiodarone, mexiletine, procainamide		
Chemotherapy	Cytarabine, ifosfamide, tacromilus, vincristine	Cytarabine, ifosfamide	Thalidomide
Dopamine-blocking and -depleting agents	Cinnarizine, haloperidol, metoclopramide, thioridazine, reserpine, tetrabenazine	—	Cinnarizine, metoclopramide, neuroleptics (e.g., haloperidol, thioridazine), reserpine, tetrabenazine
Recreational agents	Cocaine, ethanol, MDMA, nicotine	—	Cocaine, ethanol, MDMA, MPTP
Hormone treatments	Calcitonin, sex steroids, thyroxine, (medroxy)progesterone, tamoxifen	Epinephrine	(Medroxy)progesterone
Immunosuppressants	Cyclosporine, tacrolimus, interferon-alpha	Cyclosporine, tacrolimus	Cyclosporine
Metals	Arsenic, lead, mercury	—	Lead, manganese, mercury
Miscellaneous agents	Metoclopramide, cimetidine, theophylline, caffeine, cyanide	—	Metoclopramide
Toxins	Organochlorine pesticides	—	Methanol
Withdrawal syndromes	Cannabis, ethanol	—	—

MAOI, monoamine oxidase inhibitor; MDMA, methylenedioxymethamphetamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropryidine; SSRI, selective serotonin reuptake inhibitor.

improvement after withdrawal of the toxin depends on the severity and duration of exposure.

Metabolic Disorders

Almost any metabolic derangement may be associated with tremor. Thyrotoxicosis is the most common, producing an enhanced physiologic tremor. It affects any age group and responds to treatment of the underlying disorder, but it can also be ameliorated by propranolol. Tremor and myoclonus are seen frequently in Hashimoto encephalopathy. Tremor is one of the first and most prevalent signs of hypoglycemia and may be seen in nonketotic hyperglycemia along with myoclonus, chorea, and dystonia. In renal insufficiency, a postural and action tremor is often evident before asterixis develops, and may foreshadow encephalopathy. The tremor in Wilson disease may be postural, kinetic, or at rest. A coarser movement of the upper limb ("wing beating" tremor) also occurs. It is present in the proximal arms and occasionally the head in the flexion–extension plane, and is due to thalamocapsular and cerebellar system pathologic processes. Chelation therapy and liver transplantation can reverse the neuropathologic process, but there is no effective symptomatic treatment. Hemochromatosis is associated with tremor, parkinsonism, and dementia due to iron deposits in the basal ganglia; progression may be forestalled by phlebotomy or liver transplantation. Variegate porphyria and the hyperadrenergic state associated with pheochromocytoma may also cause tremor, as can striatal injury in the setting of hypoxic-ischemic encephalopathy.

Hypomagnesemia and hypocalcemia may lead to tremor, muscle twitching, and irritability, and a severe, movement-associated, distal flapping tremor may occur in hypercalcemia due to hyperparathyroidism. Tremor has been reported with hyponatremia and its correction. Severe vitamin E deficiency may cause tremor in addition to spinocerebellar findings and peripheral neuropathy, and tremors may respond to vitamin E supplementation. In infants, vitamin B_{12} deficiency can produce a generalized tremor syndrome and mental retardation, which are partially reversible with supplementation, although the abnormal movements may transiently increase with treatment before resolving.

Infections

Viral encephalitides are probably the most common infections to cause tremor (Table 58-2). Generalized tremors have also been described with poliovirus infection, St. Louis encephalitis, and the rhombencephalitis that sometimes complicates hand-foot-and-mouth disease (due to enterovirus 71). Respiratory syncytial virus encephalitis and mumps, with a predilection for the cerebellum, manifest as intention tremor and ataxia. Echovirus 21 encephalitis and Japanese encephalitis result in tremor through basal ganglia and cerebellar involvement. Herpes zoster–related vasculitis affecting the midbrain may result in an ipsilateral cerebellar syndrome with intention tremor. Congenital cytomegalovirus infection and rubella and adult tickborne meningoencephalitis result in longlasting neurologic dysfunction, including tremor. The encephalopathy sometimes present with Lassa fever may be accompanied by tremor, seizures, and coma. Meningoencephalitic involvement with flaviviruses may cause tremor in addition to the typical dengue hemorrhagic fever. A similar picture is seen in Bolivian hemorrhagic fever caused by Machupo virus (family Arenaviridae), which responds to ribavirin.

Tremor disorders occur rarely in early HIV infection but occur in 5 to 44 percent of those with HIV-associated dementia. Tremor may be part of an HIV-related parkinsonian syndrome or may occur in isolation. Typically, there is a symmetric postural tremor but there may be a rest component; kinetic components are rare. Holmes (rubral) tremor, in which rest, postural, and kinetic components are present, has been reported in AIDS and often results from opportunistic infections such as tuberculosis or toxoplasmosis. In addition to drug-induced tremor from dopamine-blocking drugs such as neuroleptics and antiemetics, AIDS patients may develop a reversible rest or postural tremor from trimethoprim-sulfamethoxazole. Treatment of tremor in HIV infection depends on etiology; drug-induced tremor and tremor secondary to opportunistic infection may be reversible.

Tremor occurs in up to 17 percent of those with tuberculous meningitis and 30 percent of those with tuberculomas and is usually of the postural variety. It may respond to antituberculous therapy over several weeks; if not, symptomatic treatment may be considered.

Recovery from *Plasmodium falciparum* malaria is occasionally followed by a corticosteroid-responsive encephalopathy with postural tremor, cerebellar ataxia, myoclonus, seizures, and motor aphasia. In neurocysticercosis, tremor and parkinsonism are the most frequent movement disorders. Tremor is also seen in typhoid, together with altered bowel habits. Unilateral postural, kinetic, and Holmes tremor have been reported with thalamic toxoplasmosis in HIV-positive patients.

Immune Disorders

CNS lupus may include tremor among its many features. Waldenström macroglobulinemia has been associated with an asymmetric tremor and peripheral neuropathy. Basal ganglia and brainstem involvement in Behçet syndrome may result in postural tremor, and pyramidal and extrapyramidal findings. Tremor may occur as a complication of celiac disease.

In Hashimoto encephalopathy, in which myoclonus and seizures are common, 80 percent of patients have postural tremor. In patients older than 50 years with cerebellar degeneration, the etiology is paraneoplastic in about half. Intention tremor, ataxia, and dysarthria are particularly associated with anti-Yo antibodies in gynecologic cancers and anti-Hu antibodies in small cell lung cancers.

Some immune-mediated polyneuropathies, particularly those associated with IgM monoclonal gammopathy, are accompanied by a distally predominant action and postural tremor. In a case-control study, 29 percent of subjects with IgM monoclonal gammopathy of undetermined significance had tremor compared to 9 percent of controls; among the 60 with tremor, 49 had postural and kinetic tremor, 8 had rest tremor, and 3 had mixed rest and action tremor.[14] The tremor sometimes responds to immunosuppressive therapy or propranolol. A postural and kinetic tremor may follow Guillain–Barré syndrome and occur in chronic inflammatory demyelinating polyneuropathy.

Other Causes of Tremor

Postural and kinetic tremors may develop after head trauma and may be transient or permanent. Cerebral radiation and gamma-knife treatments cause postural or Holmes tremor in rare instances. A postural and intention tremor may develop during compression during dives to depths greater than 100 meters as part of the high-pressure neurologic syndrome. It usually remits on decompression but occasionally persists for several months.

Approach to Diagnosis

Rapid onset (over days to months) of tremor is atypical for essential tremor but may occur when drug induced or related to an underlying medical disorder. If no offending drug or toxin is recognized, screening blood studies should include determination of electrolyte and glucose concentrations as well as thyroid, renal, and hepatic function tests. Testing for serum cortisol, parathyroid hormone, and ceruloplasmin; 24-hour urinary copper excretion; and toxicology assays may also be necessary in individual instances. Brain MRI may be required to exclude structural causes, particularly when there are other neurologic findings or the tremor is asymmetric.

Treatment

In all cases of tremor, an underlying disorder should be sought and treated while symptomatic treatment is contemplated. Action tremor, and particularly aggravated physiologic tremor, usually responds to adrenergic blockade or primidone. Other agents, including alprazolam, atenolol, gabapentin, sotolol, and topiramate, are also useful. Benefit may also occur with nadolol, nimodipine, clonazepam, botulinum toxin A, deep brain stimulation, thalamotomy and gamma-knife or ultrasound thalamotomy. Pregabalin is sometimes helpful. Rest tremor is treated by anticholinergic agents, amantadine, and dopaminergic medications; deep brain stimulation of the globus pallidus or subthalamic nucleus may be used in patients with severe parkinsonian tremor that is refractory to medications.

Cerebellar tremor is the most difficult to treat and only occasionally improves with the treatments described above. Holmes (rubral) tremor is poorly responsive to treatment but sometimes improves with levodopa, dopamine agonists, trihexyphenidyl, or some of the medications used for essential tremor; in other instances, deep brain stimulation may be necessary.

PARKINSONISM

Parkinson disease is the most common cause of parkinsonism, but there are a number of other causes that relate to systemic disease and therefore merit discussion here.

Vascular Causes

An akinetic-rigid syndrome may occur acutely, usually after infarcts of the basal ganglia, or may develop in a delayed manner, months to years after focal, multifocal, or global ischemic events. Patients may have multiple risk factors for vascular parkinsonism, such as hypertension, diabetes, hyperlipidemia, and cigarette smoking. Unlike classic Parkinson disease, the clinical disorder usually occurs later in life (in the seventh or eighth decade) and symptoms develop more rapidly. Presentation may be with gait impairment, postural instability, and so-called lower-body parkinsonism. The findings may be symmetric or asymmetric, with limb rigidity or spasticity, hyperreflexia, and extensor plantar responses; a pseudobulbar palsy and cognitive deficits may also be present. Rest tremor is uncommon but postural tremor may occur. Brain imaging commonly shows bilateral lesions often involving the external capsule, corona radiate, thalamus, basal ganglia, substantia nigra, and pons, and there may be extensive periventricular white matter lesions. Unilateral parkinsonism may occur with infarcts of the lenticulostriate arteries involving the contralateral basal ganglia.

Only a limited number of studies have explored the treatment of vascular parkinsonism. About one-third of patients—usually those with involvement of the nigrostriatal pathways—respond to levodopa, but the level of benefit is often disappointing. Medication for secondary stroke prevention may arrest progression of parkinsonian deficits and improve the long-term prognosis.

Other vascular events such as a midbrain hemorrhage, subdural hematoma, cortical venous thrombosis, arteriovenous malformations, and giant cerebral artery aneurysm may cause parkinsonism. It has also been reported in patients with vasculitis related to various connective tissue diseases.

Medications and Bone Marrow Transplantation

Drug-induced parkinsonism is common; one population-based study found that parkinsonism was likely drug induced in 20 percent of cases. Drug-induced parkinsonism differs from Parkinson disease in that symptom onset may be rapid, often over weeks, bradykinesia is more symmetric, and tremor and postural instability are less common.[15] However, individual cases may be clinically indistinguishable from Parkinson disease. Drug-induced parkinsonism occurs most often in patients treated with D2 dopamine receptor blockers (e.g., antipsychotics and metoclopramide), monoamine depleters (reserpine or tetrabenazine), and certain calcium-channel blockers (especially cinnarizine and flunarizine). A French pharmacovigilance center reported 155 cases of drug-induced or -worsened parkinsonism between 1993 and 2009.[15] About 70 percent of the cases were observed in the first 3 months after introduction of the suspect drug, whereas 30 percent occurred after 1 year. Rigidity was the most common symptom. Antipsychotic treatment (including haloperidol, risperidone, and olanzapine) was cited in 113 cases, diazepines in 15, selective serotonin reuptake inhibitors in 12, calcium-channel blockers (flunarizine, cinnarizine, verapamil and diltiazem) in 13, H1 antihistamines in 12, valproate in 10, metoclopramide in 9, and lithium in 4. Improvement occurred after stopping the medication in 89 percent of cases. Abrupt discontinuation of dopamine-blocking medications should be avoided. In our experience, reversal of symptoms may take months or even up to a year.

Acute or subacute parkinsonism has developed from disulfiram treatment or overdose. Encephalopathy, hyperglycemia, ketosis, bradykinesia, and rest tremor may develop and may improve after disulfiram is discontinued and with supportive therapy. CT may show hypodensity and MRI shows increased T2 signal in the putamen and globus pallidus.

After bone marrow or organ transplantation, parkinsonism has developed in several patients after starting cyclosporine and resolved after discontinuing it.

Toxins

Since the recognition that 1-methyl-4-phenyl-1,2,3,6-tetrahydropryidine caused rapid-onset parkinsonism, a great deal of research has shown that factors adversely affecting energy metabolism and disposal of damaged proteins in dopaminergic neurons may cause parkinsonism. In most epidemiologic studies, prolonged exposure to pesticides (particularly insecticides and herbicides) is a risk factor for Parkinson disease.

Other toxins that have been associated with parkinsonism include polychlorinated biphenyls, carbon monoxide, cyanide, some metals (mercury and manganese), and some organic solvents (carbon disulfide, trichloroethylene, and methanol). Several of these were discussed earlier in this chapter. A disorder similar to manganism may follow intravenous methcathinone use for recreational purposes (discussed on p. 1025). Carbon monoxide toxicity results from a combination of tissue hypoxia and direct cellular toxicity especially affecting the basal ganglia. Several weeks to months after initial recovery, about 10 percent of survivors will develop parkinsonism (hypomimia, rigidity, bradykinesia but without rest tremor) that is unresponsive to antiparkinsonian medications but often regresses spontaneously within 6 months.

Methanol poisoning may cause an acute parkinsonian state, but chronic exposure has also been associated with the development of parkinsonism. Acute intoxication may cause coma. Upon recovery, visual impairment, hypophonia, rigidity, and bradykinesia develop and may respond to dopaminergic agents. Brain imaging shows hypointensity of the putamen on CT scan and hyperintense lesions of the putamen on T2-weighted MRI.

Welders are frequently exposed to manganese-containing fumes, but it remains unclear whether this is associated with the development of parkinsonism. In other circumstances, chronic manganese exposure alone or in combination with liver failure has caused extrapyramidal, parkinsonian-like syndrome. Brain MRI often shows increased signal in the globus pallidus on T1-weighted images. In some cases there is improvement after chelation therapy. This form of parkinsonism is poorly responsive to dopaminergic treatment.

Metabolic Disorders

Several metabolic conditions may mimic Parkinson disease including hypothyroidism, extrapontine myelinolysis, chronic liver failure, hemochromatosis, and Wilson disease. In Wilson disease rigidity, bradykinesia, hypophonic speech, and tremor as well as autonomic disturbances may occur. Parkinsonism has been described in liver failure from other causes. In a prospective study, 21 percent of patients with liver failure being considered for liver transplantation had parkinsonism.[16] Clinical features included rapid progression over months, symmetric akinetic-rigid syndrome, postural but not rest tremor, and early gait impairment. Serum and CSF manganese levels were elevated, and MRI showed hyperintensities involving the globus pallidus and substantia nigra resembling that seen in patients with manganese exposure (Fig. 58-1). Some of these patients responded to levodopa.

Although Goswami and colleagues found that idiopathic hypoparathyroidism was associated with basal ganglia calcifications in 107 of 145 patients, parkinsonism occurred in only 2.[9] Treatment with calcium, parathyroid hormone, and levodopa may be helpful, but treatment with vitamin D is also sometimes required. In rare instances, parkinsonism has developed in patients with hyperparathyroidism and resolved after surgery.

Acute parkinsonism has been described in patients with diabetes and uremia requiring dialysis. Cognitive impairment, dysarthria, bradykinesia, and rigidity develop over days to weeks. There is typically an elevated serum creatinine, uremia, and a metabolic acidosis. Brain CT shows hypodense lenticular nuclei, and MRI shows T1 hypointense and T2 hyperintense lesions in the putamen and globus pallidus (Fig. 58-2). The condition and imaging abnormalities may resolve with hemodialysis. Development of this syndrome has been related to preceding hypoglycemia.

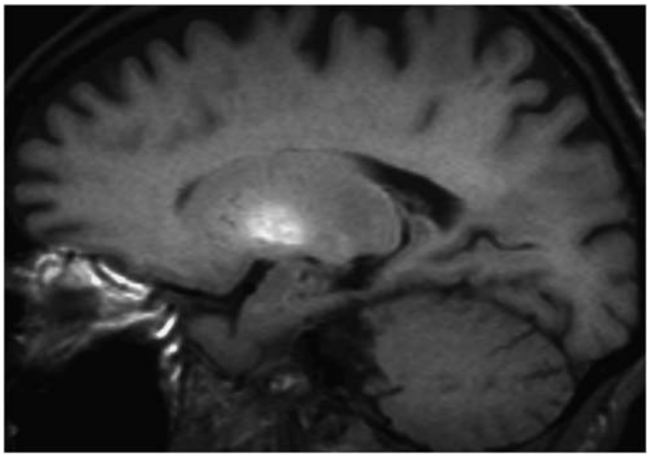

FIGURE 58-1 ■ Sagittal T1-weighted magnetic resonance image showing increased signal in the globus pallidus in a 39-year-old man with advanced liver disease due to hepatitis with a 1-year history of a gait disturbance and intermittent tremulousness. Examination showed subtle tremulousness and slowing of rapid repetitive movements in all limbs. Laboratory evaluation revealed elevated serum manganese.

Infections

Various infections may cause parkinsonism acutely or as a long-term complication (Table 58-2). Viral infections that have been associated with this phenotype include herpes simplex, HIV, Japanese encephalitis, coxsackie B, influenza A, measles (and related subacute sclerosing panencephalitis), mumps, polio, Western equine encephalitis, dengue, and St. Louis encephalitis.[17] Japanese encephalitis, prevalent in most Southeast Asian countries, is estimated to be the most common viral cause of parkinsonism. Parkinsonism or other movement disorders develop 1 to 4 weeks after the acute phase and may persist for months to years. Patients with chronic hepatitis C infection have a higher incidence of Parkinson disease than uninfected subjects.

HIV infection may cause parkinsonism by direct injury to the basal ganglia or as a consequence of immunodeficiency. AIDS-associated parkinsonism is characterized by symmetric bradykinesia, rigidity, postural instability and gait impairment; tremor is often absent. Postural and gait instability may occur early. The parkinsonism may be secondary to opportunistic infection, drug induced, or related more directly to the HIV infection. There is evidence of early involvement of the basal ganglia in HIV infection: anatomic neuroimaging reveals selective basal ganglia atrophy, and functional imaging shows relative hypermetabolism in the basal ganglia and thalamus. Neuropathologic examination frequently

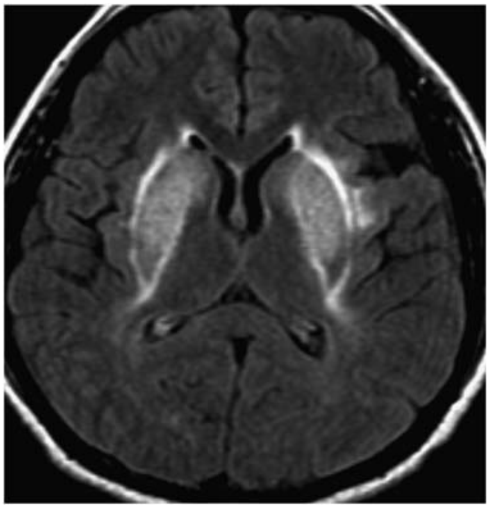

FIGURE 58-2 ■ This axial fluid-attenuated inversion recovery-weighted MRI was obtained from a 41-year-old woman with a long history of diabetes and dialysis-dependent renal failure with rapid-onset encephalopathy, dysarthria, tremor, rigidity, and bradykinesia. It shows increased signal in the putamen and globus pallidus bilaterally. Her condition improved with dialysis.

shows evidence of HIV infection with microglial nodule encephalitis affecting the putamen and caudate nuclei. Both lymphoma and opportunistic infections with *Toxoplasma* and *Cryptococcus* show an affinity for the basal ganglia. Progressive multifocal leukoencephalopathy caused by JC virus in immunosuppressed individuals may also cause parkinsonism. Perhaps because of the early involvement of the basal ganglia, HIV-infected patients develop drug-induced parkinsonism at lower doses of antipsychotic treatments.

When evaluating patients with HIV-related parkinsonism, opportunistic infection and drug-induced causes require exclusion. Treatment with dopaminergic medications may help. In some AIDS patients, parkinsonism has improved after initiation of combination antiretroviral therapy. Another patient, whose initial presentation was parkinsonism with supranuclear gaze paresis and postural instability and who did not have an AIDS-defining diagnosis but had a CD4 count of 266, reportedly improved on treatment with combined antiretroviral therapy after obtaining no benefit with levodopa.

Since the epidemic of 1916 to 1927, only sporadic cases of parkinsonism following encephalitis lethargica have been described. CSF shows a lymphocytic pleocytosis and oligoclonal bands, but bacterial and viral studies are unrevealing. Brain imaging may show inflammatory changes in the basal ganglia or brainstem. Dale and colleagues found elevated basal ganglia antibodies in 20 patients who developed parkinsonism, a sleep disorder, dyskinesia, and neuropsychiatric symptoms that were attributed to encephalitis lethargica. In 65 percent, antistreptolysin-O titers were elevated and 95 percent had basal ganglia antibodies, raising the possibility that encephalitis lethargica is an autoimmune condition possibly triggered by bacterial infection such as in Sydenham chorea.[18] In a subsequent study in children with clinical features of encephalitis lethargica, NMDA receptor antibodies were found in those with dyskinesias, agitation, and seizures but not in those with parkinsonism and somnolence.[19] Atypical cases of parkinsonism associated with NMDA receptor antibodies have been described, with amelioration by immunotherapy. Improvement may occur with methylprednisolone, with or without IVIg.

Tuberculous meningitis is a rare cause of parkinsonism. Infection with *Mycoplasma pneumoniae* is another rare cause of parkinsonism. The condition begins with a flu-like illness, and bradykinesia follows; T2-weighted MRI shows increased signal of the basal ganglia, which resolves several months after treatment of the infection. Reversible parkinsonism has been reported in Lyme disease. Other infections associated with parkinsonism, generally in association with other neurologic abnormalities, include prion disease and neurosyphilis.

Malaria and neurocysticercosis (both parasitic conditions) may cause parkinsonism and tremor. In neurocysticercosis, improvement may occur with albendazole and, when hydrocephalus is present, placement of a CSF shunt.

Autoimmune and Paraneoplastic Disorders

Parkinsonism may occur as a complication of systemic lupus erythematosus; rigidity and akinesia are more common than tremor, and pyramidal signs may be present. In a case series of 41 patients with CNS lupus, 2 presented with parkinsonism and responded to immunosuppressant (but not dopaminergic) treatment.[5] In addition to the common findings of recurrent oral and genital ulcerations, bilateral posterior uveitis and retinal vasculitis, skin papules, parkinsonism, and postural tremor have been observed in Behçet syndrome. Nonvasculitic autoimmune inflammatory meningoencephalitis may present with rapidly progressive myoclonus, dementia, and parkinsonism that improves with high-dose corticosteroids. The EEG may show persistent periodic sharp waves reminiscent of Creutzfeldt–Jakob disease. Parkinsonism has been described as a rare complication of the antiphospholipid antibody syndrome. The brain MRI shows periventricular white matter changes and the condition responds poorly to levodopa.

Paraneoplastic parkinsonism (with bradykinesia, rigidity, and tremor) and eye-movement abnormalities have been described in patients with anti-Ma2 antibodies, which are often associated with paraneoplastic limbic or brainstem encephalitis. Parkinsonism has been reported in association with the CRMP-5 antibody (although chorea is more common) and the antineuronal nuclear autoantibody type 2, and rarely with NMDA receptor antibodies as discussed earlier. Finally, parkinsonism occurs in approximately 10 percent of patients with voltage-gated potassium channel antibodies.

Trauma

Development of parkinsonism after a single head injury is rare; it typically follows severe injury with loss of consciousness. Symptoms may develop over several months. Neuroimaging usually demonstrates a lesion of the globus pallidus or substantia nigra. Parkinsonism may be secondary to chronic subdural hematoma, typically developing within weeks of the causal injury. Complete or near-complete remission of parkinsonism often follows drainage of the hematoma.

Parkinsonism may occur after repeated head injury, as in boxing. A variable spectrum of signs and symptoms may be present, including behavioral changes, dementia, and corticospinal and cerebellar deficits; dysarthria is especially common, and parkinsonism occurred in 18 of 48 subjects with recurrent head injury in one series.[20] Pathologic examination revealed atrophy of the cerebral hemispheres, medial temporal lobe, thalamus, mammillary bodies, and brainstem. Histologic examination showed extensive tau-immunoreactive neurofibrillary tangles, astrocytic tangles, and spindle-shaped neuritis. The disorder was distinguished from other tauopathies by its patchy distribution and the preferential involvement of the superficial cortical layers.[20] Patients often respond to dopaminergic treatment. The relationship of nonrepetitive remote head trauma to Parkinson disease is controversial and unsettled.

Other Causes of Parkinsonism

Some aspects of parkinsonism may be simulated by communicating or noncommunicating hydrocephalus or a subdural hematoma. In normal-pressure hydrocephalus, gait abnormalities predominate. Mass lesions are rare causes of parkinsonism. Parkinsonism resulting from focal irradiation of the brain or brainstem may respond to dopaminergic treatment and is sometimes partially reversible.

Approach to Diagnosis

Rapid onset of parkinsonism over days to months is atypical of Parkinson disease but occurs when drug induced, after infection, due to a structural brain injury (subdural hematoma, stroke, or hydrocephalus), or secondary to an underlying medical condition. If no offending drug or toxin can be identified, screening blood tests should be performed (blood electrolyte and glucose levels, erythrocyte sedimentation rate, and antinuclear antibody, as well as thyroid, renal, and hepatic function tests). Testing for 24-hour urinary copper excretion and serum ceruloplasmin determination should be considered in patients younger than 40 years. Toxicologic screening tests may be necessary in individuals for whom no cause is found. Brain imaging, particularly MRI, may be helpful.

Treatment

The management of secondary parkinsonism depends on the cause but generally includes symptomatic measures. The most common cause is medication related. When possible, the offending medication should be tapered to prevent worsening of any underlying psychiatric disorder for which it may have been prescribed and also to reduce the risk of precipitating a tardive movement disorder. When a behavioral disorder requires a dopamine-blocking agent, it is sometimes possible to switch to an antipsychotic medication with less affinity for the D2 receptor, such as clozapine or quetiapine. It may take weeks to many months for the full effect of a dopamine-blocking drug such as haloperidol to resolve.

In other cases of secondary parkinsonism, management of the underlying medical disorder may take precedence. In many cases, however, treatment of the primary disorder is inadequate and symptomatic therapy is appropriate. In general, treatment of parkinsonism with levodopa, dopamine agonists, or both, may improve bradykinesia, rigidity, or tremor. The effectiveness of dopaminergic treatment varies considerably between conditions. Other agents that may be particularly useful for tremor include amantadine and anticholinergic agents. Deep brain stimulation of the globus pallidus or subthalamic nucleus may be considered in selected patients who are refractory to medications.

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CHAPTER

59

Headache in General Medical Conditions

MORRIS LEVIN

ASSOCIATION OF HEADACHE AND GENERAL MEDICAL ILLNESS
SPECIFIC MEDICAL DISEASES AND HEADACHES
  Cardiovascular Disease
  Hypertension
  Cerebrovascular Disease
  Infectious Disease
  Thyroid Disorders
  Obesity
  Pulmonary Disease
  Renal Disease
  Hepatic Disease
  Autoimmune Disorders
  Neoplastic Disease
  Transplantation
  Psychiatric Disorders
GENERAL CONSIDERATIONS IN ADDRESSING HEADACHES IN THE ELDERLY
CONCLUDING COMMENTS

Headache disorders are very common, and therefore they often co-exist with one or more significant medical illnesses. This pairing can complicate the diagnosis of both the headache disorder and general medical conditions, while raising a number of treatment conflicts. In patients with multiple complex medical conditions, management decisions can be difficult. However, if the clinician is armed with an understanding of the key features of common headache disorders as well as a good basic background in clinical pharmacology, a successful approach to managing headaches in these patients is possible. This chapter will summarize epidemiologic observations regarding the co-occurrence of headaches and medical illnesses, explore the ways in which medical illness and headaches co-exist, and describe specific considerations regarding treatment of headaches in particular medical disease states.

ASSOCIATION OF HEADACHE AND GENERAL MEDICAL ILLNESS

Headache is the most common category of neurologic disease, and it has been estimated that around half of the world's adult population have experienced head pain in the last 12 months. Therefore, the comorbidity of headache with other medical illnesses is not surprising. For example, migraine has significant comorbidity with asthma and allergic conditions such as rhinitis, food allergies, hay fever, and bronchitis (Table 59-1). Migraine also seems to be more prevalent in people with gastrointestinal (GI) conditions such as peptic ulcer disease, hiatal hernia, and colitis, but the confounding factor of analgesic medication effects on the GI tract may complicate this relationship. There is suggestive evidence that hyperthyroidism and hypothyroidism are more commonly associated with migraine than would be predicted, and these patients should be screened for headaches at regular medical visits. All headache disorders are likely more prevalent in obesity, and worsening migraine frequency ("migraine chronification") is more common in those who are obese. Among the autoimmune disorders, celiac disease, Raynaud phenomenon, and systemic lupus erythematosus (SLE) are comorbid with migraine, as are chronic fatigue syndrome and fibromyalgia.[1,2]

Migraine, especially with aura, increases the risk of stroke, although evidence tends to be conflicting, with substantial differences seen across age groups and genders.[3] There is no clear epidemiologic association between migraine and epilepsy, although spells of each can be mistaken for one another. Recent data suggest

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TABLE 59-1 ■ Medical Conditions in Which Headache Disorders Are More Common

Anemia
Asthma
Celiac disease
Chronic fatigue syndrome
Fibromyalgia
Human immunodeficiency virus (HIV) infection
Hyperthyroidism
Hypothyroidism
Leukemia
Malignant hypertension
Obesity
Chronic pulmonary disease
Raynaud syndrome
Renal failure
Chronic rhinitis
Systemic lupus erythematosus
Rheumatoid arthritis
Psychiatric disease including depression, anxiety, and bipolar affective disorder

that migraine is an independent risk factor for developing multiple sclerosis, but the pathophysiology that would link these two conditions is uncertain. Psychiatric comorbidity with migraine and other headache disorders has long been noted and there do seem to be significant bidirectional risks in patients with anxiety, depression, and bipolar disorder. There is a well-established increased co-occurrence of headache disorders in patients with sleep disorders, with probable bidirectional causality, since pain certainly can disrupt sleep, and sleep deprivation is a common trigger for headaches. Interestingly, little evidence exists for a higher prevalence of migraine in people with hypertension despite this common belief. There is an unclear association between migraine and ischemic heart disease, with the best evidence for an association being found in young women and in those who have migraine with aura.[4] The association between migraine and patent foramen ovale (PFO) has been noted, especially in patients with migraine with aura, although there is no evidence that PFO closure improves the severity or frequency of migraine.

In children, similar associations between headache disorders and medical illness have been noted. In particular, depression, anxiety, and sleep disorders are more common in children and adolescents with migraine and there does seem to be, unlike in adult populations, an increase in headache disorders in patients with epilepsy. In children and adolescents, attention deficit hyperactivity disorder (ADHD) and Tourette syndrome are comorbid with migraine, as are PFO, cardiovascular disease, and stroke.[5]

Underlying mechanisms by which medical illnesses might cause headaches include: (1) activation of dormant migraine or other primary headache disorders; (2) production of painful cranial or pericranial inflammation as a component of the underlying medical condition; (3) irritation or compression of cranial or pericranial nociceptive nerves; and (4) medication or other treatments causing headache as an adverse effect (Table 59-2).

In the other causal direction, headache conditions can lead to or exacerbate medical illnesses via the use

TABLE 59-2 ■ Common Medications and Substances Known to Cause Headache

Alcohol
Amantadine, levodopa
Antihypertensive medications including nifedipine, enalapril, hydralazine
Carbon monoxide
Cyclophosphamide
Estrogen, progesterone, tamoxifen
Food additives (monosodium glutamate, aspartame)
Illicit drugs including cocaine, marijuana, amphetamines
Interferons
Interleukin inhibitors
Monoamine oxidase inhibitors (e.g., phenelzine)
Nitric oxide donors (e.g., isosorbide, nitroglycerin)
Nonsteroidal anti-inflammatory analgesics (NSAIDs)
Phenothiazines
Pseudoephedrine, sympathomimetics
Ranitidine, famotidine, cimetidine
Selective serotonin reuptake inhibitors
Sildenafil, vardenafil, tardalafil
Tetracyclines, trimethoprim
Theophylline
Medication overuse of opioids, barbiturates, NSAIDS, simple analgesics, and combinations such as aspirin, acetaminophen
Substance withdrawal from opioids, barbiturates, benzodiazepines, cannabis, caffeine, estrogen

(or overuse) of medications employed in preventing or alleviating headache attacks. Examples include nonsteroidal anti-inflammatory drugs (NSAIDs) leading to GI irritation, ulceration, and bleeding; corticosteroid-induced complications such as bone necrosis; exacerbation of vascular disease by ergot medications; worsening of asthma by β-blockers; renal and hepatic toxicity from a number of headache prophylactic medications; and dependency and addiction to opioids and other analgesics. Medication interactions that result from simultaneously treating headache and general medical disorders are also common and can lead to systemic illness. Headache disorders can lead to a deterioration in general health by reducing activity, worsening sleep function, limiting social involvement, and causing financial stress.

SPECIFIC MEDICAL DISEASES AND HEADACHES

Cardiovascular Disease

Patients with coronary artery disease commonly experience headaches as a consequence of vasodilating medications used for cardiovascular benefit. Attempting to reduce the dose and frequency of these drugs can improve headache control. Treating primary headache disorders in patients with cardiovascular disease poses unique challenges. Ergots are contraindicated due to their vasoconstrictive effects, which are especially prominent in patients with co-existing peripheral vascular disease. NSAIDs used for headache can reduce the benefits of antithrombotics used to treat coronary artery disease and may also lead to an increased risk of myocardial infarction via unclear mechanisms.

A number of medications used in headache management can prolong the QT interval, leading to a risk of torsade de pointes. Commonly used agents in headache treatment that share this propensity include tricyclic antidepressants, dopamine blocking agents (including prochlorperazine, metoclopramide, chlorpromazine, and promethazine), and ondansetron. Patients with a tendency for palpitations and tachyarrhythmias should probably avoid tricyclic antidepressants, and patients with bradyarrhythmias should avoid β-blockers. All patients with cardiac conduction issues should use β-blockers and calcium-channel blockers carefully and only after careful consideration by their cardiologist. In the appropriate patient, β-blockers may be useful for both migraine prophylaxis and angina reduction.

A headache type termed "cardiac cephalalgia" is a relatively rare but important entity, as it can signal the onset of acute coronary disease. The mechanism for the head pain is not clear, although it is perhaps related to an unusual pattern of referred pain. The headache is notable that it resolves with antianginal medication.

Approximately 25 percent of the population has a PFO and the prevalence seems to be nearly double that in patients with migraine. Larger PFOs are found in persons who experience migraine with aura compared with those without aura. Based on observational data showing improvement in migraine following PFO closure for other reasons, it was suggested that PFO closure could help in preventing migraine attacks. However, a randomized controlled study examining PFO closure for migraine was negative, and people with migraine and PFO should not use closure as a means of controlling their headache frequency.

Hypertension

While hypertension alone seems not to be associated particularly with headache disorders, rapidly rising and malignant hypertension is commonly accompanied by head pain, reported by some to be posteriorly predominant. The presence of this headache can serve as an early indication for more aggressive blood pressure control to prevent hypertensive complications such as hypertensive encephalopathy, which itself is virtually always accompanied by headache in awake, communicative patients. The very small number of severely hypertensive patients who harbor an underlying pheochromocytoma will also commonly present with headaches, often highly unresponsive to treatment.

In hypertensive patients, posterior reversible encephalopathy syndrome can occur from the blood pressure rise itself, and the initial presentation may include, or even be limited to, headache. A possibly related condition, reversible cerebral vasoconstriction syndrome (RCVS) can occur in a number of settings including pregnancy and typically presents with one or more sudden severe thunderclap headaches. RCVS is diagnosed using noninvasive imaging which typically reveals multiple areas of intracerebral arteriolar narrowing, often with evidence of focal, cortical subarachnoid hemorrhage.

Some antihypertensive medications can be very useful in preventing migraine, including propranolol, atenolol, and nadolol. Angiotensin-converting enzyme inhibitors do not have significant antimigraine properties, but the angiotensin receptor blocker candesartan can be an efficient agent for patients with both hypertension and migraine. Verapamil and amlodipine are particularly useful in limiting cluster headache attacks, although the dosage used must often be high.

Some antihypertensives have the tendency to worsen headaches, including the calcium-channel blocker nifedipine and some of the angiotensin-converting enzyme inhibitors. Treatment with triptans is contraindicated in patients with severely elevated blood pressure as they can worsen hypertension, but they are considered to be generally safe in hypertensive patients with good blood pressure control by medications.

Cerebrovascular Disease

It has long been known that headache can be a common presentation for stroke, both ischemic and hemorrhagic, in addition to more traditional focal neurologic symptoms and signs. A vexing problem is the distinction between migraine aura with minor or no headache and transient ischemic attack (TIA). Positive visual phenomena are the most common migraine aura and include scintillations, oscillating "zig-zag" lines, and wavy vision; this presentation is rare in TIA. In some elderly patients with visual phenomena from migraine, there may be no history of headache, a condition termed "late-life migrainous accompaniments." While transient sensory loss, aphasia, and hemianopic loss of vision are common TIA symptoms, they also can occur as part of a migraine aura. Some of these patients are misdiagnosed as having a stroke and are commonly treated as such with the intravenous administration of thrombolytics. A progression of sensory changes beginning distally and progressively moving centrally is very suggestive of migraine aura rather than stroke, as is the short duration of most auras, which usually last less than 30 minutes. Motor auras are quite rare in migraine, and can be compelling for a TIA diagnosis. Monocular vision loss is extremely unlikely in migraine.

In patients with a history of stroke who require acute migraine treatment, ergots are contraindicated, as they are in cardiovascular and peripheral vascular disease. Triptans, as weak vasoconstrictors, are generally considered contraindicated in patients with cerebrovascular disease, but this concern is probably exaggerated and not supported by strong evidence.

Infectious Disease

Infections which lead to meningeal inflammation typically produce significant head pain. Some purely systemic infections are also known to induce headache or exacerbate primary headaches, often for unclear reasons. These patients with systemic bacterial and viral infections tend to respond to simple analgesics, or when severe, limited opioid treatment. In contrast, patients will often experience a particularly prolonged and refractory headache after successful treatment of their underlying meningitis or encephalitis.

Some headaches accompanying infectious diseases may represent an exacerbation of a pre-existing primary headache disorder such as migraine, but there are a number of secondary headaches that must be considered in this setting, including septic venous sinus thrombosis, which carries a high mortality and presents often with head pain. Intracranial abscesses may present with headache particularly when their size increases.

Human immunodeficiency virus (HIV) is known to affect the central nervous system and may induce meningeal inflammation leading to head pain, but the virus itself may also lead to chronic headaches without evidence of meningitis for unclear reasons.[6] Virtually all of the antiretroviral agents used to treat HIV can cause headache. Careful adjustment of dosing and trials of alternative agents usually allow HIV treatment to proceed without headache.

Several areas of caution must be observed when treating HIV patients for primary headache disorders. Divalproex may lead to increased replication of HIV and should be avoided. Ergots and some triptans including almotriptan, eletriptan, and naratriptan are CYP3A4 substrates, and therefore coadministration with protease inhibitors may significantly increase the risk of severe vasoconstriction. Other triptans should be safer including rizatriptan, sumatriptan, and zolmitriptan. Other agents that are CYP3A4 substrates, including calcium-channel blockers, should be used cautiously. Topiramate, an inducer of CYP3A4, could lower the concentration of protease inhibitors.

Postlumbar puncture headaches are generally managed with judicious hydration and caffeine administration followed by lumbar epidural blood patching when the pain is refractory. In severe cases, patients can present with a dramatic postural headache that is worse when sitting or standing and can even occasionally develop subdural hematomas from stretching of the bridging veins due to sagging of the brain within the cranial vault.

Focal paranasal sinus infections commonly produce headaches. Bacterial and fungal etiologies predominate, and often surgical resection is necessary for relief of pain while antimicrobial treatment is ongoing. Occasionally, headache represents intracranial extension of these infections, and the development of cranial nerve abnormalities or a particularly refractory headache should prompt neuroimaging.

Thyroid Disorders

Headaches are more common in both hypothyroid and hyperthyroid states, even when the altered thyroid status is subclinical.[7,8] These headaches can mimic migraine and often respond to treatment of the underlying thyroid condition. Graves disease can additionally lead to pain via the direct inflammation and heightened nociception produced by the ophthalmopathy it can cause from involvement of the eye muscles themselves. Hyperthyroidism has also been associated with several other neurologic conditions which themselves may present with headache including cerebral venous sinus thrombosis and intracranial hypotension.

Lithium carbonate, highly effective in some cases of cluster headache, can reduce the production of T4 as well as interfere with the deiodination of T4 to produce T3. Therefore thyroid status must be carefully monitored in any patient taking lithium for primary headache disorders, particularly in those known to have pre-existing thyroid dysfunction.

Obesity

Evidence suggests that obesity and migraine are comorbid and that women with migraine in particular are more likely to experience weight gain.[9,10] Headache preventive medications that promote additional weight gain, such as tricyclic antidepressants, gabapentin, neuroleptics, and divalproex, should be avoided in obese patients. In some cases topiramate, which leads to weight loss for many patients, might be of use for both headache prevention and body mass index reduction. This topiramate-induced weight loss can continue unabated in some patients, leading to an unhealthy reduction in weight which requires careful monitoring.

Pulmonary Disease

Headaches are observed in many patients with chronic pulmonary disease, in part because of hypoxia, a known trigger for headache. Asthma is comorbid with headache and must be identified since nonselective β-blocker medications are contraindicated for migraine prophylaxis in these patients. The cardioselective β-blockers atenolol and metoprolol are sometimes tolerated in these patients. Bronchodilators used to treat asthma can induce migraine, and new headache in the setting of a change in inhaler prescription should be a clue to this association. Sedatives such as benzodiazepines and opiates may depress respiratory drive and should be avoided in patients with pulmonary disease if possible.

Patients with obstructive sleep apnea often report morning headaches. The phenomenon was previously thought to be the result of insufficient cerebral oxygenation. However, whether hypoxia, carbon dioxide retention, or other factors lead to these headaches upon awakening is now a matter of debate. Successful treatment of the underlying sleep disorder seems to improve headache in many patients.[11] Clues to the presence of obstructive sleep apnea when evaluating a patient with headache include the three cardinal manifestations of heavy snoring, gasping during the night, and daytime somnolence; cognitive complaints can also be a useful warning sign.

Renal Disease

Headaches are common in patients with chronic kidney disease. A number of metabolic triggers have been implicated as the etiology of headache in end-stage renal disease (ESRD) including hyperkalemia and hypomagnesemia. Headache is the most common neurologic symptom reported by hemodialysis patients (~50%), generally occurring during or soon after dialysis and resolving within 72 hours after dialysis. The pain is usually bilateral and in most patients is only very brief. Factors that raise the likelihood of dialysis headache include hypertension, elevated blood urea nitrogen, low serum osmolality, and low magnesium. Caffeine withdrawal may be the cause in some patients as caffeine is removed during dialysis. Headaches are also seen in the dialysis disequilibrium syndrome (see Chapter 16) which consists of headache, cerebral swelling, seizures, stupor, and coma.

Preventing dialysis headache can be challenging. Recommendations include chlorpromazine 25 to 50 mg orally given prior to dialysis, or prophylactic nortriptyline or magnesium supplementation. Other suggested beneficial interventions include volume maintenance, blood pressure control, and avoidance of caffeine dependence.[12,13]

Treating headaches pharmacologically in patients with chronic renal failure must be performed carefully as some medications may be poorly excreted, leading to toxicity. Other medications with high protein-binding affinity are poorly dialyzable and might need to be avoided. Tricyclic antidepressants, β-blockers and anticonvulsants such as topiramate can be used within recommended guidelines in ESRD patients.

For mild head pain, acetaminophen is preferred over NSAIDs due to the latter's potentially toxic effects on the kidney. Triptans seem safe in ESRD; eletriptan or frovatriptan should be used preferentially as these are not eliminated renally. Ergots are considered contraindicated in these patients. If opioids are used, they should be used sparingly, as accumulation can lead to respiratory depression and seizures. Codeine, hydrocodone, meperidine, morphine, and tapentadol should probably be avoided. If needed, hydromorphone may be the best choice as it is relatively short acting, has safe metabolites, and is not heavily protein bound.

Hepatic Disease

Liver disease, outside of florid hepatic encephalopathy, is not known to cause headaches. However the presence of liver disease can be a contraindication to the use of some common treatments for migraine and other headache disorders due to concern regarding further hepatic injury. Potentially culprit medications include acetaminophen, tricyclic antidepressants, divalproex, topiramate, carbamazepine, oxcarbazepine, calcium-channel blockers, and neuroleptics. Patients with liver disease, including those with concomitant occult alcoholism, should have hepatic enzyme levels monitored frequently if one of these medications is selected for headache treatment in order to avoid further hepatic compromise. Medications that are metabolized by the cytochrome P-450 pathway, including benzodiazepines, calcium-channel blockers, corticosteroids, ergots, carbamazepine, ondansetron, and some triptans (primarily eletriptan and almotriptan), may build to toxic levels in patients with advanced liver disease, and patients should therefore be monitored closely for side effects.

Autoimmune Disorders

It was formerly believed that patients with SLE were much more likely to experience migraine-like headaches, termed "lupus headaches," than the general population. This phenomenon has not been demonstrated conclusively in population-based studies, so the relative prevalence of headaches in SLE is not clear.[14] The antiphospholipid syndrome has not been shown to be comorbid with migraine.

Cerebral vasculitis in SLE is rare, but when it occurs, it is very painful. Polyarteritis nodosum and other arteritides that affect the central nervous system are very likely to produce headaches, often directly related to inflammatory vascular changes. Pain can occur diffusely or focally, and usually requires strong analgesics. It has been suggested that people with Raynaud phenomenon are more likely to have migraine.

Rheumatoid arthritis commonly produces cervicogenic headaches due to its tendency for atlanto-axial deformation leading to C2 and C3 radicular pain as well as local upper cervical periosteal and ligamentous pain, all of which can produce a focal or diffuse headache via pain referral mechanisms. These headaches tend to be worsened by provocative neck maneuvers and can sometimes be ameliorated with physical therapy.

Neoplastic Disease

For a multitude of reasons, patients with noncranial cancer experience frequent headaches. Chemotherapeutic agents often are the direct causes of headaches, and anemia, thrombocytosis, leukocytosis, and erythrocytosis all produce headache whether as part of the neoplastic disease process or its treatment. Anorexia and sleep deprivation are common headache triggers, and the stress of investigations and treatments in many cancer patients triggers migraine and other underlying headache disorders. When headache is persistent and new, cranial metastases, including meningeal carcinomatosis, as well as infectious meningitis must be aggressively ruled out with imaging and likely cerebrospinal fluid sampling.

Brain and skull tumors are known to produce headaches, via either the mechanism of dural stretching due to large tumor size or due to hydrocephalus. Pituitary region tumors, even when small, may lead to migraine- or cluster-like headaches. Seizures, nausea, vomiting, and focal neurologic signs and symptoms are common with brain tumors. Surgical resection generally helps to reduce headache frequency, and radiation therapy has also been shown to be effective in controlling head pain.

Many chemotherapeutic agents are substrates for the cytochrome P-450 system and therefore a headache medication that induces this system might pose a risk for reduction in efficacy of these agents. Commonly used headache medications that potentially have this effect include carbamazepine, oxcarbazepine, topiramate, dexamethasone, and prednisone.

Transplantation

Antirejection medications tend to be metabolized by P-450 systems. Hence, migraine medications which are inducers of this system will potentially lower the levels of these antirejection drugs and inhibitors may raise them to toxic ranges. Renal transplant recipients should probably avoid NSAIDs and hepatic transplant patients might want to avoid divalproex, topiramate, tricyclic antidepressants, and calcium-channel blockers given their organ-specific deleterious effects.

Psychiatric Disorders

There is a complex interplay between head pain and mood disorders. The increased co-occurrence of migraine and depression, anxiety, and bipolar disorder

TABLE 59-3 ■ Common Migraine and Other Headache Medications that are Known to Exacerbate Medical Illnesses

Medication	Key Medical Illness(es)	Effects
Tricyclic antidepressants	Arrhythmia	Tachycardia
	Obesity	Increased appetite
	Orthostatic hypotension	Syncope
	Prostatic hypertrophy	Urinary retention
	Gastrointestinal dysmotility	Constipation
	Epilepsy	May lower seizure threshold
	Liver disease	May cause enzyme elevation
β-Blockers	Cardiac disease	AV nodal blockade
	Diabetes	Poor response to hypoglycemia
	Asthma	Bronchoconstriction
	Orthostatic hypotension	Syncope
	Depression	May worsen depression
Calcium-channel blockers	Arrhythmia	Tachycardia
	Liver disease	May cause enzyme elevation
Divalproex	Liver disease	May cause enzyme elevation
Topiramate	Liver disease	May cause enzyme elevation
Gabapentin	Obesity	Weight gain
Lithium	Cardiac disease	Arrhythmia
	Hypothyroidism	Exacerbates hypothyroid state
NSAIDs	Bleeding disorder	Increases bleeding
	Renal disease	Worsens renal function
	Peptic ulcer disease, gastritis	Worsens or causes ulcers
Triptans	Cardio/cerebrovascular disease	May cause vasoconstriction
	Hypertension	May elevate blood pressure
Ergots	Cardio/cerebrovascular disease	Likely cause vasoconstriction
	Peripheral vascular disease	Peripheral vasoconstriction
Neuroleptic antiemetics	Liver disease	Liver enzyme elevation
	Obesity	Weight gain
CGRP monoclonal antibodies	Gastrointestinal dysmotility	Constipation
Corticosteroids	Obesity	Weight gain
	Diabetes	Hyperglycemia
	Gastritis	Peptic ulcer disease
	Immunosuppression	Infections

are suggestive of causality, but confounding genetic, treatment-related, and social factors make firm epidemiologic conclusions elusive.[15] Pain is demoralizing, and framing it in this manner is probably the most compassionate approach to the patient with mood alterations. Both psychiatric and headache disorders must be treated optimally and concurrently in order to benefit the patient. Some clinicians have attempted to use a parsimonious approach, attempting the treatment of both with one medication. This may be successful by happenstance, but more useful is a coherent attempt by the neurologist and the psychiatrist working together to improve both conditions. Since many psychiatric medications will have interactions with migraine medications, medication dosage adjustment and timing decisions must be made carefully.

Substance abuse can be a confounding factor in headache disorders as well as in many psychiatric conditions. Understanding local substance use patterns and availability and being observant for signs of dependence and addiction are of the utmost importance. Urine toxicology screens can be useful diagnostically as well as to monitor those in remission.

GENERAL CONSIDERATIONS IN ADDRESSING HEADACHES IN THE ELDERLY

The differential diagnosis of headaches in the elderly requires careful attention. These patients can have many concurrent medical problems and these might cause headache either directly or from medications used to treat these disorders. The rate of secondary unsuspected causes of head pain rises throughout adulthood, and therefore thoughtful investigation is important. Some headache types seem to affect the older age demographic almost exclusively, including temporal arteritis and an interesting primary headache variety, "hypnic headache," a benign but annoying nighttime headache which is responsive to small doses of caffeine prior to sleep.

Migraine and other primary headache disorders can affect the elderly, who pose treatment challenges due both to their comorbid illnesses and due to their aging physiologic states. Migraine medications will interact with other medications and doses may need to be reduced due to a higher propensity for adverse effects. Sedation and alterations in cognition are potentially life-threatening adverse effects as is ataxia due to the propensity for falls, and therefore medications with these side effects should be used judiciously. Elderly patients commonly have other painful conditions that predispose them to overuse of analgesics, which may lead to both toxicity and an increased incidence of medication overuse headache.

CONCLUDING COMMENTS

Migraine and other primary headache disorders frequently become problematic in patients with concurrent medical conditions. Systemic medical illnesses themselves may directly cause head pain due to the disease process or its treatment. New headaches are always worth pursuing aggressively, looking for underlying causes, as are headaches that are accompanied by focal neurologic symptoms or signs or those that occur in the setting of systemic illnesses causing head and neck inflammation or central nervous system dysfunction. Treating primary or secondary headaches in medically ill patients poses challenges due to treatment effects on underlying illnesses as well as drug interactions (see Table 59-3). A careful, thoughtful approach to these patients is typically effective, with gratifying results in pain management and quality of life.

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CHAPTER 60

Neuromuscular Complications of General Medical Disorders

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DISORDERS OF THE MOTOR NEURON

RADICULOPATHY

DISORDERS OF POSTERIOR ROOT GANGLIA

PLEXOPATHY

PERIPHERAL NEUROPATHY
- Focal Neuropathy
- Multifocal Neuropathy
  - *Vasculitic Neuropathy*
  - *Idiopathic Immune-Mediated Multifocal Neuropathy*
  - *Sarcoidosis*
  - *Infectious Neuropathy*
- Polyneuropathy
  - *Endocrine Neuropathy*
  - *Infectious Neuropathy*
  - *Immune-Mediated Neuropathy*
  - *Critical Illness Polyneuropathy*
  - *Uremic Neuropathy*
  - *Neoplastic and Paraneoplastic Neuropathies*
  - *Nutritional Neuropathy*
  - *Toxic Neuropathy*
  - *Hereditary Neuropathy*

NEUROMUSCULAR JUNCTION DISORDERS
- Botulism
- Lambert—Eaton Myasthenic Syndrome
- Myasthenia Gravis
- Medications and Toxins

MYOPATHY
- Endocrine-Related Myopathy
  - *Acromegaly*
  - *Corticosteroid Myopathy*
  - *Hyperparathyroidism and Osteomalacia*
  - *Hyperthyroidism and Hypothyroidism*
- Infectious Myopathies
  - *Human Immunodeficiency Virus Infection*
  - *Viral Myositis*
  - *Other Infections*
- Inflammatory Myopathies
  - *Dermatomyositis and Polymyositis*
  - *Inclusion-Body Myositis*
  - *Necrotizing Autoimmune Myositis*
  - *Sarcoidosis*
  - *Polymyalgia Rheumatica*
- Critical Illness Myopathy
- Metabolic and Toxic Myopathies
  - *Alcohol*
  - *Hyperkalemia or Hypokalemia*
  - *Uremia*
- Medication-Induced Myopathy
- Statin-Induced Myopathy

RHABDOMYOLYSIS AND MYOGLOBINURIA

The diagnosis of disorders of the neuromuscular system involves localizing the lesion anatomically and then weighing the validity of specific diagnostic hypotheses. Symmetry and rapidity of the disease process are major diagnostic considerations. Pure motor syndromes localize to the anterior horn cells, neuromuscular junctions, or muscles, though, rarely, neuropathies can also produce pure motor deficits. Combinations of motor and sensory deficits suggest radiculopathy, plexopathy, or neuropathy.

A diagnostic strategy complementary to the aforementioned approach employs pattern matching. Neuromuscular diseases present with one of five basic patterns (Table 60-1). Weakness is usually a more prominent feature of demyelinating than axonal neuropathies.

In general, electromyography (EMG) and nerve conduction studies (NCSs) are essential for confirming the anatomic localization, differentiating axonal from demyelinating neuropathies, and making

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TABLE 60-1 ■ Classification of Neuromuscular Diseases by Presentation Patterns

Acute Generalized Weakness
Guillain–Barré syndrome
Botulism
Necrotizing myopathy
Tick paralysis
Severe electrolyte imbalance
Periodic paralysis
Subacute or Chronic Generalized Weakness
Amyotrophic lateral sclerosis
Demyelinating motor neuropathies
Myopathy
Myasthenia gravis
Slowly Progressive, Generalized Weakness More Than Numbness
Demyelinating polyneuropathy
Slowly Progressive, Distal Numbness More Than Weakness
Axonal polyneuropathy
Numbness, Weakness, or Pain Limited to One Limb
Radiculopathy
Plexopathy
Entrapment neuropathy
Initial nerve involved by vasculitic neuropathy

Adapted from McCarthy RJ, Olney RK: Neuromuscular disease. p. 287. In Corey-Bloom J (ed): Diagnosis-Based Adult Neurology. Mosby, St. Louis, 1997.

prognostic statements. Decisions concerning the need for muscle or nerve biopsies should be deferred until electrodiagnostic testing is completed.

DISORDERS OF THE MOTOR NEURON

Amyotrophic lateral sclerosis (ALS) is the most common and prototypic motor neuron disease. It presents with flaccid weakness and atrophy of muscles without associated pain or sensory disturbances. Degeneration of upper motor neurons also occurs, producing spasticity and hyperreflexia in wasted limbs. Most cases are sporadic, but approximately 10 percent are inherited in autosomal-dominant or -recessive patterns. The pathogenesis of ALS is not known, but it is possible that multiple pathogenic mechanisms are at play, including impaired cellular handling of oxidative stress, neuroinflammation, neurotrophic factor deficiency, glutamate-induced excitotoxicity, and defects in protein metabolism and autophagy. There is no cure for ALS, although riluzole and edavarone modestly slow progression of disease.[1] Noninvasive ventilation, careful nutritional monitoring and supplementation, and multidisciplinary care can improve the quality of life. A sporadic clinical variant characterized by solely lower motor neuron involvement (progressive muscular atrophy) is managed similarly.

Hereditary anterior horn cell diseases include spinal muscular atrophy (SMA), Kennedy syndrome, and hexosaminidase A deficiency. Biallelic mutations or deletions in the *SMN1* gene cause SMA. The copy number of a nearly identical gene, *SMN2*, on the same chromosome as *SMN1* determines the disease severity and age of onset. Intravenous *SMN1* gene replacement using a viral vector and an intrathecally administered antisense oligonucleotide therapy have been approved for this condition.[2,3] Kennedy disease (spinal and bulbar muscular atrophy) is an X-linked disease characterized by proximal muscle weakness, muscle atrophy, and fasciculations, especially periorally. Affected individuals often have gynecomastia and testicular atrophy with reduced fertility. Expansion of a CAG repeat in the androgen receptor gene is responsible.

Compression of the spinal cord may result in segmental loss of anterior horn cells. In cervical spondylosis, combined injury to both the anterior horn cells and descending corticospinal tracts may occur, leading to atrophy and weakness in the hands combined with spastic paraparesis; such a presentation mimics that of ALS.

Many viruses have central nervous system (CNS) tropism, but only a few strains cause acute and selective loss of anterior horn cells. Poliovirus is an enterovirus spread via a fecal–hand–oral route. Most patients are either asymptomatic or develop only mild constitutional symptoms. More severe signs and symptoms may occur in nonparalytic poliomyelitis, and the cerebrospinal fluid (CSF) findings are often indicative of aseptic meningitis. Individuals developing acute paralytic poliomyelitis experience constitutional symptoms but also develop rapidly progressive weakness over the course of one to a few days. Weakness is often focal and asymmetric in the limbs or bulbar muscles, but may be symmetric or generalized. It frequently improves over several weeks to months. Rarely, the live-attenuated oral poliovirus vaccine can cause paralytic poliomyelitis. In the United States, an inactivated poliovirus vaccine is used, which does not carry the risk of vaccine-associated poliomyelitis.

Postpolio syndrome consists of slowly progressive new or worsened weakness, together with fatigue or pain in the muscles or joints, typically occurring many years after acute paralytic poliomyelitis in about 20 to 40 percent of individuals. The pathogenesis may involve late denervation of previously reinnervated muscle fibers or musculoskeletal abnormalities.

Viruses other than poliovirus, such as West Nile virus (WNV), echovirus, coxsackievirus, herpes zoster virus, and Epstein–Barr virus may also cause loss of motor neurons. Only about 20 percent of WNV infections are symptomatic, usually manifesting as a febrile illness. A maculopapular rash is common. About 1 percent of infected individuals develop neurologic symptoms that may include meningoencephalitis, flaccid paralysis, or both. As in poliovirus infection, the weakness is often proximal and asymmetric, with no significant sensory abnormalities. The CSF shows a lymphocytic or neutrophilic pleocytosis (30 to 150 cells/mm^3) and high protein content. CSF and serum should be screened for IgM antibodies to WNV. Adding WNV polymerase chain reaction (PCR) testing of both the serum and CSF can increase the diagnostic yield. Treatment is supportive. Rarely, WNV may present with brachial plexopathy, rhabdomyolysis, or a predominantly demyelinating polyneuropathy similar to Guillain–Barré syndrome (GBS).

Paraneoplastic lower motor neuron involvement may occur rarely with lymphoproliferative disorders, thymoma, and various cancers (bronchial, ovarian, renal, and prostate). Patients may have anti-Hu (ANNA-1) and anti-Yo (PCA-1) antibodies, CSF protein level is often elevated, and there is a variable CSF pleocytosis. The weakness may improve after treatment of the cancer.

RADICULOPATHY

Pain or numbness in a dermatomal pattern accompanied by weakness in a segmental pattern suggests a radiculopathy. External compression is the most frequent cause of nerve root injury, by either intervertebral disc herniation or spondylosis. Radiculopathy resulting from degenerative spine disease is discussed further in Chapter 22. Other causes of radiculopathy may include gouty spine disease, Paget disease, Tarlov cysts, and methylacrylate extrusion during spine surgery. Extradural tumors such as schwannomas, neurofibromas, and meningiomas may also produce a radiculopathy. A radiculopathy sometimes results from epidural or spinal anesthesia; the injury may result from direct trauma to the nerve or from chemical injury related to the injected substance.

Diabetic thoracoabdominal radiculopathy (diabetic truncal neuropathy) is a common cause of noncompressive radiculopathy. Patients present with pain and hyperalgesia in a region along the chest or abdomen. The pattern of involvement may be clearly dermatomal, but often the changes span more than one segment. Segmental weakness may manifest as an outpouching of the abdominal wall. The pathophysiology is unclear, but an inflammatory vasculopathy may be responsible.

Compression of multiple lumbosacral nerve roots produces a cauda equina syndrome, which may lead to permanent urinary and fecal incontinence and lower extremity weakness and numbness and thus constitutes a neurosurgical emergency. The usual cause is a large, midline disc herniation. Chronic cauda equina syndrome may be caused by a developmental anomaly, such as a tethered spinal cord.

Spondylosis is the most common cause of polyradiculopathy, although metastatic spinal disease should also be considered. Cancers of the breast, lung, prostate, or kidney, or multiple myeloma metastasize most frequently to the spine. Polyradiculopathy results from direct tumor compression or from leptomeningeal infiltration of the roots by tumor cells (neoplastic meningitis). Treatment of spinal bony metastases often involves external beam irradiation, although decompressive surgery may be necessary in radiation-resistant tumors.

Carcinomatous meningitis often affects the caudal roots first. Cranial neuropathies, meningeal signs and symptoms, and a myelopathy may be associated features. CSF analysis typically shows a pleocystosis, hypoglycorrhachia, elevated protein level, and malignant cells on cytologic analysis. The yield of positive cytology for malignant cells is increased significantly by repeating the lumbar puncture. Treatment is usually palliative and includes radiation therapy and intrathecal chemotherapy. The median survival of patients with leptomeningeal metastases is 4 months.

Infectious causes of polyradiculopathy include cytomegalovirus (CMV), *Borrelia burgdorferi* (Lyme disease), Epstein–Barr virus, herpes simplex virus, *Mycobacterium tuberculosis*, and *Treponema pallidum*. CMV polyradiculopathy usually presents as a late complication of acquired immunodeficiency syndrome (AIDS), but it can be a presenting manifestation of human immunodeficiency virus (HIV) infection. The onset of flaccid paraparesis, lower extremity numbness, and urinary retention may be acute or subacute. A neutrophilic pleocytosis on CSF analysis is a clue to the diagnosis; the diagnosis is confirmed by a culture or CMV DNA PCR assay on CSF. Treatment includes ganciclovir, foscarnet, or both.

Arachnoiditis is a nonspecific term for inflammation of the spinal leptomeninges. Historically, arachnoiditis has been associated with tuberculous and syphilitic meningitis and with obsolete oil-based contrast agents for myelography. Currently, the term often refers to the appearance of thickened meninges and clumping of the nerve roots on magnetic resonance imaging (MRI) of the spine, usually in patients who have undergone lumbar spine surgery. There is controversy about the association of the imaging findings, clinical findings, and symptoms. Arachnoiditis has also been described in association with toxoplasmosis and subarachnoid hemorrhage; sometimes the cause is not known.

DISORDERS OF POSTERIOR ROOT GANGLIA

Diffuse or regional impairment of tactile sensation or gait ataxia without weakness suggests degeneration of posterior root ganglia cells (sensory neuronopathy). Patients may also have facial numbness and autonomic involvement, manifesting as gastroparesis, orthostatic hypotension, sexual impairment, and Adie pupils. EMG and NCSs differentiate sensory neuronopathies from more common distal sensory axonal polyneuropathies. Sensory neuronopathies may be acquired (Table 60-2) or hereditary.

TABLE 60-2 ■ Disorders of Posterior Root Ganglia

Autoimmune
Autoimmune chronic active hepatitis
Paraneoplastic syndrome
Sjögren syndrome
Idiopathic
Infectious
Epstein–Barr virus infection
Human immunodeficiency virus infection
Rickettsia conorii infection
Varicella zoster infection
Nutritional
Nicotinic acid deficiency
Pyridoxine deficiency
Vitamin E deficiency
Toxic
? Antibiotic-related
Cisplatin
Pyridoxine
Thalidomide

Paraneoplastic sensory neuronopathy (see Chapter 27) is commonly associated with small cell lung cancer but also occurs with breast or ovarian cancer, Hodgkin lymphoma, neuroendocrine tumors, and sarcoma. Symptom onset is generally subacute. Antibodies to the Hu antigen (ANNA-1) are usually present, but their absence does not exclude the possibility of paraneoplastic sensory neuronopathy. Antibodies to the collapsin response-mediator protein 5 (CRMP5) have also been described in some patients with small cell lung cancer. Sensory neuronopathy may occur with other paraneoplastic syndromes. Management is directed to the diagnosis and treatment of the underlying cancer. Treatment of the paraneoplastic condition with intravenous immunoglobulin (IVIg), plasmapheresis, or other immunosuppressive therapies is often disappointing.

Autoimmune or inflammatory conditions associated with sensory neuronopathy (sometimes as the initial manifestation) include Sjögren's syndrome and autoimmune hepatitis. The posterior root ganglia of patients are infiltrated by T lymphocytes. IVIg and plasmapheresis have benefited some patients.

An acute sensory neuronopathy syndrome characterized by the acute onset of widespread sensory symptoms, areflexia, impaired vibratory sensation, and gait ataxia has developed 4 to 12 days after initial antibiotic treatment for a febrile illness. The underlying pathogenesis in such cases may be infectious, postinfectious, or toxic (related to antibiotic use).

Infectious causes of sensory neuronopathy are shown in Table 60-2. HIV infection may cause a sensory neuronopathy. T-cell infiltration of dorsal root ganglia has been found in patients with end-stage AIDS. Many of these patients also have pallor of the cervical portion of the gracile tract at autopsy, suggesting that a "dying-back" axonopathy occurs along with sensory neuron loss.

Latent infection of the dorsal root ganglia occurs following primary varicella zoster virus infection. When cell-mediated immunity is compromised, reactivation of viral replication causes the clinical syndrome of herpes zoster. The elderly, transplant recipients, and HIV-positive patients are particularly vulnerable. The prodromal stage of herpes zoster includes fevers, dysesthesias, and malaise. Several days later, a vesicular eruption appears in a dermatomal distribution. Pathologically, there is intense inflammation of the dorsal root ganglia. Once the lesions become encrusted, they are no longer infectious. Approximately 3 percent of patients develop segmental paresis, perhaps from spread of the virus to the anterior horn cells. Most patients recover muscle strength with time. Treatment during the early stages of infection includes acyclovir, valacyclovir, or famcyclovir. Postherpetic neuralgia may occur, particularly in the elderly. Tricyclic drugs or anticonvulsants are effective treatments, as discussed in Chapter 42. Patients age 50 and older with a history of herpes zoster and immunocompetent patients age 60 or older without a history of herpes zoster should receive the zoster vaccine.

A number of toxins and vitamin deficiencies cause sensory neuronopathy. Because many of these also cause an axonopathy, they are discussed later (pp. 1071–1073).

Hereditary sensory neuronopathy (hereditary sensory and autonomic neuropathy) is both genetically and phenotypically heterogeneous; some forms present with predominantly small-fiber involvement, whereas others have mixed small- and large-fiber involvement. There is variable involvement of the autonomic nervous system. Commercial genetic testing is available for some types.

PLEXOPATHY

Trauma and compression, including at childbirth, cause most plexus injuries; other causes include tumor infiltration, postirradiation injury, and infection. An autoimmune monophasic neuritis, often idiopathic but sometimes associated with diabetes mellitus, may involve portions of either the brachial or lumbosacral plexus.

Sports, motorcycle, and industrial accidents cause traction injury to the brachial plexus. If the arm is located at the side of the patient at the time of impact or is distracted away from the torso, the upper roots and plexus are preferentially injured. If the arm is elevated above the head, the lower trunks and roots are most vulnerable. Compression injury of the brachial or lumbosacral plexus may occur during surgery or coma or from mass lesions such as a hematoma or tumor.

Immune brachial plexopathy (brachial plexus neuritis, neuralgic amyotrophy, Parsonage–Turner syndrome) is an acute monophasic neuropathy that presents with severe shoulder pain accompanied by muscle weakness and atrophy. Both sporadic and hereditary forms exist. Proximal muscle groups are more commonly affected than distal ones; involvement may be either unilateral or bilateral. Sensory loss is mild. Ipsilateral diaphragmatic weakness sometimes occurs from phrenic nerve involvement. Nerve biopsy specimens have revealed perineurial thickening and perivascular inflammatory infiltrates. Corticosteroids or IVIg, or both, have been used in treatment with anecdotally reported success, but controlled studies are needed. Aggressive treatment to control pain is important. The prognosis is excellent, with 60 percent of patients recovering completely within 1 year and 80 percent within a few years.

Nondiabetic lumbosacral radiculoplexus neuropathy refers to a similar disorder that affects the lower extremities. As with immune brachial plexus neuropathy, pain is often the initial symptom. It may occur in the back, buttock, thigh, or leg. Proximal weakness is more common than distal weakness. In time, however, the weakness often becomes more diffuse in the limb, and bilateral involvement is common. Clinically, sensory deficits (despite the pain) tend to be relatively mild. Nerve biopsies have shown evidence of ischemic injury and epineurial perivascular inflammatory collections. Some improvement in strength occurs with time but long-standing motor deficits are common. Case reports suggest a potential benefit of corticosteroids, plasmapheresis, or IVIg therapy, but no positive controlled trials have been published. Diabetic lumbosacral radiculoplexopathy (proximal diabetic neuropathy; diabetic amyotrophy) is discussed in Chapter 19.

Breast and lung cancers are the two most common secondary neoplasms to infiltrate the brachial plexus. Gastrointestinal and genitourinary cancers, melanomas, and lymphomas may also metastasize to the brachial plexus. Colorectal cancer is the most common neoplasm to infiltrate the lumbosacral plexus, but uterine, prostate, and ovarian cancer may also do so; other neoplasms may spread to the lumbosacral plexus metastatically.

Radiation therapy that includes the plexus in the field (as for breast cancer) may produce delayed weakness, dysesthesias, and numbness in the affected limb (Chapter 28). Irradiation causes marked fibrosis of the nerve fibers, loss of myelin, and destruction of the vascular supply. The period between the radiation treatment and onset of symptoms ranges from a few weeks to more than 30 years. Paresthesias in the median-innervated digits are a common initial symptom. Subsequently, weakness of the intrinsic hand muscles develops. Prominent limb pain and a Horner syndrome suggest tumor involvement rather than radiation-induced injury, whereas the presence of fasciculation potentials and myokymia on needle EMG suggests radiation injury. Distinction of these two disorders is aided by MRI.

Patients with radiation-induced lumbosacral plexopathy have generally been treated for lymphoreticular, testicular, uterine, or ovarian cancer. Patients usually present with slowly progressive distal weakness; numbness or paresthesia is less common. Mild pain occurs in 50 percent of patients. The CSF protein concentration may be elevated. As with radiation-induced brachial plexopathy, the condition may stabilize, but patients are often disabled.

Finally, a lower motor neuron syndrome affecting the legs, with relatively intact sensation, may also occur following irradiation of the distal spinal cord and cauda equina. Patients have generally received more than 40 Gy. Pathologic examination of the cauda equina shows a vasculopathy of the proximal nerve roots. Although the condition eventually stabilizes, patients are usually left with significant disabilities. There is no treatment.

Neurogenic thoracic outlet syndrome occurs when an anomalous fibrous band between the first thoracic rib and a cervical rib or elongated transverse process on the seventh vertebral body exerts pressure on the first thoracic nerve root or the lower trunk of the brachial plexus. This leads to wasting and atrophy of the hand muscles, particularly of the thenar eminence, and intermittent pain and paresthesias of the inner arm and medial hand, including the fourth and fifth digits. Electrodiagnostic studies confirm the diagnosis. A chest x-ray may show the cervical rib or an elongated transverse process (Fig. 60-1); the fibrous band shows up as a radiolucency. MRI may be helpful in showing and localizing plexus involvement (Fig. 60-2). Treatment is surgical.

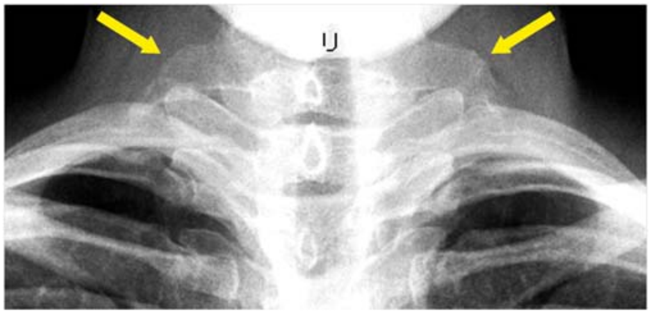

FIGURE 60-1 ▪ Chest radiograph of a 31-year-old right-handed woman with slowly progressive wasting and weakness of the left hand and numbness along the medial left forearm and hand. Bilateral cervical ribs are present (*arrows*). This finding may be associated with the neurogenic thoracic outlet syndrome. A fibrous band originating from the cervical rib compresses the inferior elements of the brachial plexus, leading to a wasted hand.

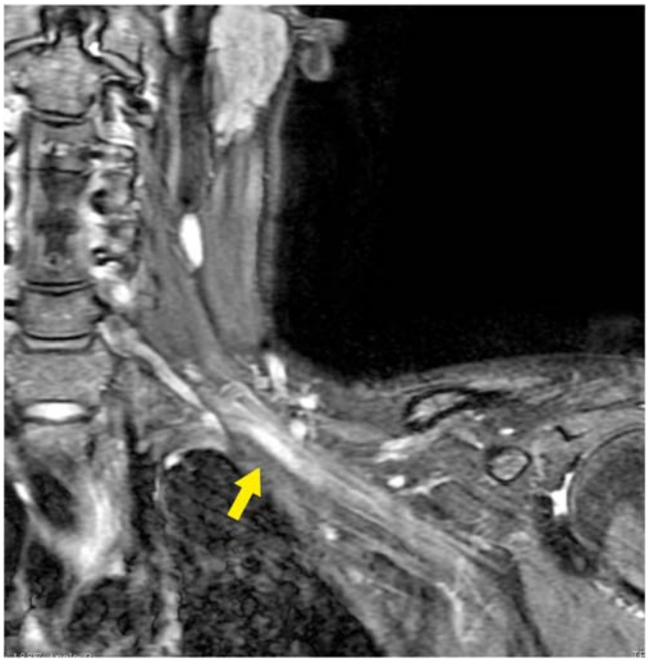

FIGURE 60-2 ▪ Coronal T2-weighted magnetic resonance image (MRI) of the left brachial plexus from the same patient as in Fig. 60-1. There is increased signal in the left lower trunk (*arrow*), illustrating the usefulness of MRI for localizing nerve trunk lesions.

PERIPHERAL NEUROPATHY

The distribution of findings may suggest either a focal, multifocal, or generalized/symmetric pattern of nerve involvement. For the multifocal and generalized neuropathies in particular, identifying the relative involvement of motor and sensory fibers (Tables 60-3 to 60-5) narrows the differential diagnosis. Sensory neuropathies may be further subdivided according to whether predominantly large- or small-diameter fibers are affected (Tables 60-4 and 60-5). Knowing whether the pathogenesis is predominantly axonal or demyelinating (Tables 60-6 and 60-7) also refines the diagnostic search. Generally, patients with axonal neuropathies present with predominantly sensory signs and symptoms, whereas patients with demyelinating neuropathies have more significant weakness. Given the exceptions to this rule, however, NCSs must be performed to distinguish between these two possibilities. Finally, the time course of symptom onset has important implications for

TABLE 60-3 ■ Causes of Acquired Peripheral Neuropathy With Predominantly Motor Involvement

Inflammatory and Infectious
Chronic inflammatory demyelinating polyradiculoneuropathy
Guillain–Barré syndrome
Infectious mononucleosis
Multifocal motor neuropathy
Metabolic
Diabetic lumbosacral radiculoplexopathy (diabetic amyotrophy)
Porphyria
Neoplastic
Lymphoma
Toxic
Dapsone
Lead
Mercury
Nitrofurantoin
Organophosphates

TABLE 60-4 ■ Causes of Acquired Peripheral Neuropathy With Predominantly Large-Fiber Sensory Loss

Connective tissue disorder (especially Sjögren syndrome, systemic lupus erythematosus)
Diabetes mellitus
Monoclonal gammopathy
Nutritional
Vitamin B_{12} deficiency
Vitamin E deficiency
Pyridoxine deficiency
Paraneoplastic (associated with anti-Hu antibody)
Renal failure
Toxic
Cisplatin
Pyridoxine
Nitrous oxide
Glutethimide

pathogenesis (Table 60-8). Discussion here focuses on those peripheral neuropathies associated with systemic diseases.

TABLE 60-5 ■ Causes of Acquired Peripheral Neuropathy With Predominantly Small-Fiber Sensory Loss

Metabolic
Amyloidosis
Early diabetic polyneuropathy
Fabry disease
Renal failure
Tangier disease
Infective
Human immunodeficiency virus infection
Leprosy
Toxic
Chloramphenicol
Ethanol
Metronidazole
Other
Sensory neuritis of Wartenberg
Sensory perineuritis

Focal Neuropathy

A focal neuropathy may occur wherever ischemia, trauma, compression, injection, infection, or tumor infiltration affects the nerve. Focal *ischemic neuropathies* are uncommon following brief acute arterial occlusion. An exception to this rule is acute ischemic fibular (peroneal) neuropathy after thrombosis or embolism of the superficial femoral or popliteal arteries. The patient presents with a cool, pulseless distal lower extremity, sudden pain in the calf or foot, and footdrop. The nerve's susceptibility is related to the common occurrence of a single arterial feeder at the lateral aspect of the knee. Once circulation is restored, recovery may take weeks but is often good. Arterial insufficiency may lead to chronic ischemic neuropathies. Brachial artery to cephalic vein shunts placed for hemodialysis have been associated with median, ulnar, and radial neuropathies. A vascular steal syndrome seems to be a major mechanism of nerve injury, but direct compression of nerves and distal limb edema may also play a role.

Benign *tumors* of nerves (schwannomas and meningiomas) usually present as sporadic, solitary tumors with or without neurologic signs or symptoms. In a patient with multiple such lesions, however, neurofibromatosis

TABLE 60-6 ■ Acquired Symmetric Length-Dependent Axonal Polyneuropathy Associated With Systemic Disease

Drugs
Amiodarone
Chemotherapeutic agents [Adriamycin (doxorubicin), Taxol (paclitaxel), vincristine]
Dapsone
Disulfiram
Hydralazine
Isoniazid
Metronidazole
Nitrofurantoin
Phenytoin
Tricyclic antidepressants
Endocrine
Acromegaly
Diabetes mellitus
Hypothyroidism
Infectious
Hepatitis B
HIV infection
Lyme disease
Mononucleosis
Tick paralysis
Metabolic
Critical illness
Hyperglycemia
Hypoglycemia
Hypophosphatemia
Renal failure
Neoplastic and Paraneoplastic
Amyloidosis
Leukemia
Lymphoma
Monoclonal gammopathy
Small cell lung cancer
Nutritional
Deficiency of vitamin B_1, B_6, B_{12}, or E or of copper
Vitamin B_6 intoxication
Toxins
Acrylamide
Arsenic
Carbon disulfide
Ethanol
Industrial toxins
Lead
Mercury
Methylbutyl ketone
Thallium
Triorthocresylphosphate
Trauma
Cold
Mechanical
Radiation

TABLE 60-7 ■ Acquired Demyelinating Neuropathy Associated With Systemic Diseases

Acute
Acute arsenic poisoning
Diphtheria
Guillain–Barré syndrome
Subacute and Chronic
Chronic inflammatory demyelinating polyradiculoneuropathy
Monoclonal gammopathy
Monoclonal gammopathy of undetermined significance
Multiple myeloma
Cryoglobulinemia
Waldenström macroglobulinemia
POEMS syndrome (osteosclerotic myeloma)
Lymphoma
Lymphoproliferative Disorder
After allogenic stem-cell transplant for malignancy
Toxins
Checkpoint inhibitors
n-Hexane
Tacrolimus

should be suspected. An enlarging lesion or the development or progression of neurologic signs should raise suspicion of malignant transformation.

The common *entrapment* neuropathies—median neuropathy at the wrist, ulnar neuropathy at the elbow, and fibular (peroneal) neuropathy at the fibular head—share anatomic factors that increase the susceptibility of the nerve to injury; these factors include superficial nerve location, adjacent bony structures, and enclosure by nonelastic connective tissues. External compression of nerves generally causes focal demyelination before significant axonal loss.

Various medical conditions contribute to carpal tunnel syndrome (CTS; median nerve entrapment at the wrist), the most common compressive neuropathy. Diabetes mellitus is a major risk factor. The pathogenesis of CTS in this context may relate to chronic endoneurial hypoxia and changes in the connective tissues of the nerve sheath or transverse carpal ligament. Hypothyroidism and acromegaly are also associated with CTS. In acromegaly, edema of synovial tissues may cause nerve compression. In pregnancy (Chapter 31), edema and weight gain contribute to increased pressure

TABLE 60-8 ■ Cause of Peripheral Neuropathy in Relation to Onset and Time Course

Acute Onset (Hours to Days)
Compression
Diphtheria
Guillain–Barré syndrome
HIV infection
Ischemia
Lyme disease
Porphyria
Tick paralysis
Toxic (e.g., arsenic)
West Nile virus infection
Subacute Onset (Weeks to Months)
Infectious
Inflammatory and immune disorders
Metabolic
Nutritional
Paraneoplastic
Toxic
Chronic (Years)
Amyloidosis
Chronic inflammatory demyelinating polyradiculoneuropathy
Diabetes mellitus
Hereditary neuropathy
Monoclonal gammopathy
Monophasic
Guillain–Barré syndrome
Herpes zoster
Inflammatory ganglionopathy
Single toxic exposure
Relapsing
Hereditary neuropathy with liability to pressure palsy
Inflammatory and immune disorders (chronic inflammatory demyelinating polyradiculoneuropathy, monoclonal gammopathy, connective tissue disorders)
Porphyria
Refsum disease
Repeated toxic exposure

in the carpal tunnel. Rheumatoid arthritis is the most important inflammatory condition associated with CTS. Rheumatoid nodules, wrist deformity, and tenosynovitis are all contributory factors. When CTS accompanies a distal symmetric polyneuropathy in a nondiabetic patient, amyloidosis should be considered. If such patients undergo carpal tunnel surgery, fat and ligament tissue should be sent to pathology for analysis for possible amyloid deposition. Other risk factors for CTS include female sex, ganglion cysts, lipomas, nonspecific tenosynovitis, gout, sarcoidosis, multiple myeloma, aromatase inhibitors, and hereditary neuropathy with liability to pressure palsies. Repetitive hand motions in certain occupations may also be contributory. Conservative management of CTS includes the nocturnal use of wrist splints to prevent wrist flexion or extension (which reduces pressure within the carpal tunnel) or oral or injected corticosteroids. For severe neuropathies or for those in whom conservative measures have failed, surgical release of the carpal tunnel is effective.

The evaluation and management of the other common entrapment neuropathies are discussed in standard neurologic texts.

Multifocal Neuropathy

Most multifocal neuropathies are immune mediated or infectious (Table 60-9). The immune-mediated forms may be idiopathic, triggered by an infection or toxin/medication, or associated with diabetes mellitus. The most severe presentation is the acute and catastrophic appearance of multiple mononeuropathies (mononeuritis multiplex) caused by systemic vasculitis.

VASCULITIC NEUROPATHY

Vasculitic neuropathy is an ischemic neuropathy caused by obliteration of the nerve's nutrient blood vessels by inflammatory infiltrates. It usually presents as a subacutely evolving, asymmetric, painful sensory or sensorimotor neuropathy. Often, the deficits are in the distribution of multiple individual nerves (mononeuropathy multiplex). Nerves in the lower extremities are often affected first, but any nerve may be involved. Over time in untreated patients, as additional nerves become injured, motor and sensory deficits may become confluent, thereby mimicking a polyneuropathy. Sometimes, as in the case of cryoglobulinemic vasculitic neuropathy, the initial presentation of a vasculitic neuropathy is symmetric.

Neuropathy may occur with primary vasculitis, in which the underlying cause is not known, or secondary vasculitis, in which the causative factor is identified. The

TABLE 60-9 ■ Causes of Multifocal Neuropathy
Infection
Diffuse infiltrative lymphocytosis syndrome
Herpes zoster
Human immunodeficiency virus infection
Leprosy
Lyme disease
Syphilis
Tuberculosis
Ischemia
Vasculitic neuropathy
Systemic necrotizing vasculitis
Vasculitis associated with connective tissue diseases (rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus)
Vasculitis associated with infections (hepatitis B and C, HIV)
Medication-induced vasculitis
Nonsystemic vasculitic neuropathy
Diabetes mellitus (diabetic lumbosacral radiculoplexus neuropathy, diabetic mononeuropathies)
Idiopathic Immune-Mediated Neuropathy
Idiopathic brachial plexopathy
Graft-versus-host disease
Multifocal acquired demyelinating sensory and motor neuropathy (Lewis–Sumner syndrome)
Multifocal motor neuropathy
Sarcoidosis
Sensory neuritis of Wartenberg
Sensory perineuritis
Multiple Compressions and Entrapments
Amyloidosis
Neurolymphomatosis
Rheumatologic conditions
Trauma
Tumors
Genetic Conditions
Hereditary neuropathy with liability to pressure palsy
Porphyria

primary systemic vasculitides are classified according to size of the damaged blood vessels, organs involved, and the suspected immunopathologic mechanisms at play. Polyarteritis nodosa, microscopic polyangiitis, granulomatosis with polyangiitis (Wegener granulomatosis), and eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) are the primary systemic vasculitides most commonly associated with vasculitic neuropathies. The most common vasculitic neuropathy is an idiopathic form similar to polyarteritis nodosa and microscopic polyangiitis but without overt systemic involvement, called nonsystemic vasculitic neuropathy. Because these patients do not have a defined connective tissue or other systemic disease, the diagnosis is established by nerve biopsy. Most of these patients have an elevated erythrocyte sedimentation rate, and a minority are anemic with peripheral leukocytosis and thrombocytosis. Secondary vasculitis may be associated with connective tissue diseases, infections, neoplasms, medications, or toxins.

Given the broad differential diagnosis of vasculitic neuropathy, the laboratory evaluation is extensive and often includes a complete blood count and erythrocyte sedimentation rate; examination for antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies, complement levels, and hepatitis B and C serologies; urinalysis with microscopic analysis; and renal and hepatic function tests. The work-up may also include an HIV antibody test, chest x-ray, and Lyme antibody studies. An electrodiagnostic study is essential to document the multifocal nature of the axon loss. A nerve biopsy is often necessary for diagnosis. For the systemic vasculitides, the diagnostic yield is increased if biopsy is performed on both the nerve and muscle.

The systemic vasculitides are often fatal if untreated, so aggressive immunosuppression with combined corticosteroids and cyclophosphamide is usually indicated. When vasculitis is caused by drugs, removal of the offending agent often leads to benefit. For vasculitis associated with chronic viral infections, treatment often includes antiviral therapy or removal of viral antigens by plasmapheresis.

Hepatitis B

Approximately one-third of cases of polyarteritis nodosa are associated with hepatitis B infection. More than 80 percent of patients with hepatitis B–associated polyarteritis nodosa have a neuropathy. Although the clinical features may be indistinguishable from classic polyarteritis nodosa, the disease manifestations of hepatitis B–associated vasculitis may be more severe. Immune complex deposition is thought to be the main immunopathologic mechanism.

Treatment of hepatitis B–related vasculitic neuropathy is specialized. Although immunosuppressive therapies lead to increased viral replication, two retrospective studies suggest that a short course of corticosteroids is beneficial. Following steroid therapy, either tenofovir or entecavir may be used. Plasma exchanges are usually given concurrently over a 10-week period to clear the immune complexes. Relapses are uncommon.

Hepatitis C

A minority of patients with hepatitis C virus (HCV) infection develop a peripheral neuropathy, sometimes associated with cryoglobulinemia. As cryoglobulinemia can cause a vasculitic neuropathy with more severe neurologic deficits, the following discussion focuses on it.

HCV is the most common cause of essential mixed cryoglobulinemia, which occurs in about one-third of patients with HCV; a cryoglobulinemic neuropathy only occurs in 2 to 3 percent of patients. Other manifestations of cryoglobulinemia include edema, palpable purpura, and membranoproliferative glomerulonephritis. The cryoglobulinemia results from an oligoclonal expansion of B-lymphocytes. Most cryoglobulinemic neuropathies are distal, axonal, and symmetric with predominantly sensory deficits. Mononeuropathies, either single or multiple, may also occur. Rarely, patients with cryoglobulinemia may develop demyelinating polyneuropathies associated with IgM binding to myelin.

Patients with HCV-associated cryoglobulinemic neuropathy should be treated with direct-acting antiviral therapy.[4] For refractory cases, immunosuppression with monoclonal anti-CD20 antibodies (rituximab) with or without corticosteroids may be necessary.

Other Infections

Any organism can produce a vasculitis if it elicits either circulating or in situ immune complexes. CMV and herpes zoster are the only two infections known to infect endothelial cells of peripheral nerve blood vessels.

HIV infection (Chapter 43) may rarely cause a systemic vasculitis. It usually occurs in the early symptomatic stage of the disease. Multiple patterns of nerve involvement have been described, including mononeuropathy, mononeuritis multiplex, cranial neuropathies, distal symmetric polyneuropathy, and asymmetric polyneuropathy. The possibility of CMV vasculitis must be excluded in this patient population. In CMV-negative cases, nerve biopsy samples show a necrotizing vasculitis that may involve the endoneurial vessels in addition to the epineurial vessels. Other causes of multifocal neuropathies in HIV patients include neurolymphomatosis and diffuse infiltrative lymphocytosis syndrome.

IDIOPATHIC IMMUNE-MEDIATED MULTIFOCAL NEUROPATHY

Immune-mediated multifocal neuropathies exist in which the target of the immunologic attack is the myelin or axon rather than the blood vessels. These entities include multifocal motor neuropathy, Lewis–Sumner syndrome (or multifocal acquired demyelinating sensory and motor neuropathy), sensory perineuritis, and migratory sensory neuropathy of Wartenberg. In some cases, there is overlap between these neuropathies and GBS and chronic inflammatory demyelinating polyneuropathy (CIDP). Because GBS and CIDP are usually associated with generalized weakness, however, they are discussed separately in a later section.

Multifocal motor neuropathy is important to recognize because it can superficially mimic motor neuron disease, and attention here is focused on this disorder. Patients typically present with painless wasting, weakness, and sometimes fasciculations of the distal upper-extremity muscle groups, although any muscle group may be affected, even the tongue. Careful examination reveals that weakness occurs in a peripheral nerve rather than segmental pattern. Upper motor neuron signs are not present. Patients may complain of mild sensory symptoms such as numbness or paresthesia, but the sensory examination is typically normal. Reflexes tend to be depressed only in regions of weakness. NCSs usually reveal conduction block in motor nerves along with normal sensory nerve conduction responses. Half of patients have elevated titers to GM1 ganglioside.

IVIg is the most effective therapy for multifocal motor neuropathy, with approximately 80 percent of patients responding to it. Its efficacy has been confirmed by multiple randomized, placebo-controlled trials. Other agents that may improve or stabilize the disease include subcutaneous immunoglobulin, cyclophosphamide, azathioprine, rituximab, and interferon-beta. Mycophenolate mofetil did not have an IVIg-sparing effect in a randomized, controlled trial. Although a few patients have been reported to respond to prednisone, it is usually ineffective or may cause an exacerbation of weakness. Plasmapheresis is usually not effective.

SARCOIDOSIS

Neurosarcoidosis is discussed in Chapter 49, to which the reader is referred.

INFECTIOUS NEUROPATHY

Lyme disease and leprosy are important causes of multifocal neuropathy and are discussed separately in Chapters 39 and 41.

Polyneuropathy

The medical disorders discussed in this section cause generalized and symmetric neuropathies. In axonal neuropathies, the sensory and motor deficits are usually length dependent such that the deficits are most severe in the feet. With long-term disease, a classic stocking-glove neuropathy occurs, with or without autonomic involvement. In demyelinating polyneuropathies, however, the weakness may involve proximal and distal muscle groups more equally.

ENDOCRINE NEUROPATHY

Diabetic Polyneuropathy

As discussed in Chapter 19, diabetes mellitus may be associated with both generalized and focal neuropathies. The focal neuropathies include lumbosacral radiculoplexus neuropathy (diabetic amyotrophy; proximal diabetic neuropathy), thoracolumbar neuropathy, entrapment neuropathies, and cranial neuropathies. The generalized neuropathies include distal symmetric sensory or sensorimotor polyneuropathy, acute painful neuropathy, autonomic neuropathy, and acute motor neuropathy.

Approximately 50 percent of diabetics develop a distal symmetric sensorimotor polyneuropathy. Risk factors for polyneuropathy include degree of hyperglycemia, duration of diabetes, age, hypertension, hypertriglyceridemia, and smoking. The association between prediabetes and polyneuropathy is a subject of active debate. A number of investigators have found an increased prevalence of impaired glucose tolerance in patients with idiopathic neuropathy. However, a careful case-control study of patients with idiopathic neuropathy did not show a significant association between prediabetes and neuropathy.

Early symptoms include distal numbness, burning dysesthesias, and allodynia in the feet or toes. Although discomfort is present throughout the day, it often worsens at night or with rest. Cramps are common in the calves and foot muscles. Treatment consists of tight glycemic control, which helps to prevent and slow the progression of the polyneuropathy. Large-scale controlled trials of aldose reductase inhibitors and nerve growth factor in the treatment of diabetic neuropathy have yielded disappointing results. Controlled trials of intravenous and oral preparations of the antioxidant α-lipoic acid have demonstrated its benefit on neuropathy signs and pain.

Other Neuropathies

Hypothyroidism is a common cause of median neuropathy at the wrist (CTS). Myxedematous tissue beneath the flexor retinaculum is thought to cause median nerve compression. Hypothyroidism may also cause a polyneuropathy that presents with distal dysesthesias and stocking-and-glove sensory loss. Reflexes may be diminished with a delayed relaxation phase. Electrodiagnostic and pathologic studies have shown mixed axonal and demyelinating features. Considerable improvement may occur in both CTS and hypothyroid polyneuropathy following replacement therapy.

Acromegaly may cause entrapment neuropathies due to connective tissue hyperplasia and bony overgrowth. A sensorimotor polyneuropathy may also occur associated with hypertrophic, sometimes palpable, nerves.

INFECTIOUS NEUROPATHY

HIV Neuropathy

As discussed in Chapter 43, HIV infection is associated with both acute and chronic, multifocal or generalized polyneuropathies. These include mononeuritis multiplex from vasculitic neuropathy, GBS, CIDP, and distal sensory polyneuropathy. Of all these neuropathies, distal sensory polyneuropathy is by far the most common, occurring in at least 50 percent of patients with advanced HIV infection. In the era before combination antiretroviral therapy, reduced $CD4^+$ lymphocyte cell counts and increased HIV viral loads increased the risk and severity of HIV polyneuropathy. Dideoxynucleoside antiretrovirals also increase the risk of neuropathy, possibly because of toxicity to mitochondria. A polyneuropathy (usually symmetric) may occur as part of the diffuse infiltrative lymphomatosis syndrome.

Patients typically present with burning dysesthesia in feet and ankles, often with prominent allodynia. On examination, small-fiber sensory modalities are affected predominantly. Weakness related to the neuropathy is uncommon, even in advanced cases. There is no specific treatment, although a number of symptomatic treatments for neuropathic pain, including gabapentin, amitriptyline, tramadol, and lamotrigine, are effective.

Other Neuropathies

HCV infection and leprosy may cause generalized and symmetric peripheral nerve involvement, as is discussed earlier in this chapter and elsewhere in this volume.

IMMUNE-MEDIATED NEUROPATHY

Guillain–Barré Syndrome

Once used interchangeably with the label *acute inflammatory demyelinating polyneuropathy*, GBS now encompasses any acute, idiopathic inflammatory polyneuropathy producing progressive muscle weakness and areflexia, regardless of whether the underlying neuropathy is demyelinating or axonal. In many cases, a respiratory or gastrointestinal illness precedes the onset of neurologic symptoms by 1 to 3 weeks. Often paresthesias in the distal limbs herald the onset of the neuropathy. Pain similar to sciatica, myalgia, or a cramp may also occur. Rapidly progressive, symmetric weakness soon follows. Typically the weakness starts in the legs, but it may begin in the arms or face. Symptoms may progress acutely over just a few days or subacutely over as long as 4 weeks. The degree of weakness at the nadir of the progressive phase is highly variable, from mild weakness to quadriplegia with respiratory failure. Maximum deficits occur within 1 month, followed by a plateau lasting for days to weeks and rarely months. Gradual improvement occurs after the plateau phase. Prognosis is good, with a 5 percent mortality rate. Permanent disabilities remain in 5 to 10 percent of patients, mild deficits in 65 to 75 percent, and no deficit in 15 percent. The annual incidence is 1 to 2 cases per 100,000 population.

The initial assessment of GBS patients should include measurements of respiratory capacity and inspiratory force. Patients with a vital capacity of less than 20 mL/kg or a maximum inspiratory pressure less than 30 cmH_2O are likely to require mechanical ventilation. These measurements are much more sensitive than arterial blood gas analysis for predicting incipient neuromuscular respiratory failure. Admission to the intensive care unit (ICU) is warranted for any patient with rapidly progressive disease, significant bulbar or facial weakness, or autonomic dysfunction. Motor findings typically outweigh sensory deficits. One-third of patients may develop facial diplegia. Stretch reflexes are hypoactive or absent.

Blood tests and a lumbar puncture should be undertaken to evaluate for other causes of acute polyneuropathy or polyradiculopathy. In 50 percent of patients, an initial CSF sample will reveal an elevated protein concentration; with subsequent analysis, 90 percent of samples show increased protein, with values ranging from 55 to 250 mg/dL. The CSF is usually acellular with normal pressure. If more than 10 white cells/mm^3 are present, alternative diagnoses should be considered. NCSs commonly show evidence of a polyneuropathy, usually demyelinating, but are sometimes normal when the patient first presents.

In Western societies, GBS is usually a demyelinating polyradiculoneuropathy (acute inflammatory demyelinating polyradiculoneuropathy; AIDP). A number of infections may trigger GBS, including CMV, Epstein–Barr virus, herpesvirus, *Campylobacter jejuni*, *Mycoplasma pneumoniae*, and HIV infection. Rabies and swine flu vaccinations, recent surgery, and pregnancy have also been implicated as triggers for GBS. Both humoral immune responses and T-cell activation are thought to play roles in the pathogenesis. Pathologically, there is the early appearance of lymphocytes surrounding nerve vessels. This is followed by demyelination. Secondary “bystander” axonal degeneration may also occur.

In northern China, the most common GBS subtype is an *acute motor axonal neuropathy* (AMAN) associated with *C. jejuni* infection. These patients often have antibodies to gangliosides, including GM1, GD1a, and GD1b. The strains of *C. jejuni* associated with AMAN have GM1-like epitopes in their lipopolysaccharide membranes that contain a Gal(b1–3)GalNac moiety. Terminal motor axon branches and the internode axonolemma also contain a high concentration of this moiety. Because of molecular mimicry between these bacterial and axon antigens, those portions of the motor axons appear to be the initial targets in the autoimmune attack.

Both AIDP and the less frequent AMAN subtype have been associated with recent Zika virus infection. The viral syndrome precedes the onset of GBS symptoms by a median of 6 days. Treatment is the same as for other presentations of GBS.

There are several other variants of GBS. The most common, the Miller Fisher syndrome, accounts for about 5 percent of all cases of GBS. Patients develop the triad of ophthalmoplegia, ataxia, and areflexia, with varying degrees of limb weakness. Almost all cases of Miller Fisher syndrome are associated with IgG antibodies to GQ1b. Other variants include pharyngeal-cervical-brachial weakness; paraparesis; bilateral facial paresis with distal paresthesias; pure ataxia; acute pandysautonomia; and acute motor–sensory axonal neuropathy. The AMAN variant is usually associated with IgG anti-GM1 antibodies. All variants have in common absent or diminished stretch reflexes, elevated CSF protein concentrations, and electrodiagnostic abnormalities.

For severe cases, treatment includes support in the ICU and immune-modulatory therapy. Plasmapheresis or IVIg is effective in improving short- and long-term neurologic function. The costs of plasmapheresis and IVIg are similar, and the relapse rate for IVIg is no different from that for plasmapheresis. Compared with plasmapheresis, IVIg is associated with fewer complications (e.g., hemodynamic fluctuations), is easier to administer, and is usually available in community hospitals where plasmapheresis may not be accessible. A combination of plasmapheresis followed immediately by IVIg does not lead to significantly better outcomes.

Corticosteroids are not beneficial.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

CIDP is a chronic neuropathy characterized by symmetric weakness, sensory loss, and depressed stretch reflexes. Weakness usually affects both proximal and distal muscle groups. The cranial nerves are rarely involved, but cranial neuropathies may be a presenting feature. A small percentage of patients have papilledema. The weakness must progresses beyond 2 months in order to meet an arbitrary criterion for the diagnosis of CIDP. The clinical course may be relapsing, progressive, or stepwise. There are a number of clinical variants of CIDP manifesting with either pure motor or sensory involvement or with evidence of only distal demyelination. CIDP may occur with certain medical disorders, including monoclonal gammopathies, inflammatory bowel disease, thyroid disease, HIV infection, diabetes mellitus, Charcot–Marie–Tooth neuropathies, and CNS demyelination. Approximately 10 percent of CIDP patients have antibodies directed against proteins expressed at the nodes of Ranvier.[5] Patients with these antibodies do not have segmental demyelination of the nerve fibers. Instead disruption of the nodal architecture blocks conduction of signals along the affected nerve fibers.

The electrodiagnostic and pathologic features are similar to those of GBS. Lumbar puncture typically reveals an acellular CSF with an elevated protein level, but other laboratory tests are unremarkable. NCSs confirm slowed nerve conduction velocities or the presence of conduction block caused by demyelination. Nerve biopsy is occasionally performed, and the findings include endoneurial perivascular inflammation with demyelination, remyelination (onion bulb formations), and secondary axonal degeneration.

Randomized, controlled trials have demonstrated the benefit of corticosteroids, plasmapheresis, subcutaneous Ig, and IVIg. A crossover study demonstrated that plasmapheresis and IVIg are about equally effective. Azathioprine, cyclosporine, mycophenolate, and cyclophosphamide are sometimes reported to be beneficial but have not been tested in controlled clinical trials. Overall, most patients respond to treatment, but relapses are common. Most patients ultimately achieve a remission. Aggressive and early treatment is warranted because unchecked disease may eventually lead to axon loss and muscle atrophy for which there is no specific treatment.

Polyneuropathy Associated With Monoclonal Gammopathy of Undetermined Significance

A monoclonal gammopathy of undetermined significance (MGUS) may present as a symmetric sensorimotor polyneuropathy with variable proportions of axonal or myelin injury. The prevalence of MGUS is 1 to 3 percent in people older than 50 years. Only a minority of those with MGUS ever develop a clinically significant neuropathy, the precise number varying in different series and depending on which heavy chain is involved. Compared with neuropathy patients having IgA and IgG MGUS, patients with IgM MGUS have more sensory ataxia and more evidence of demyelination on electrodiagnostic studies. Specific antibodies can sometimes be found to myelin-specific proteins. The CSF is acellular but the protein concentration is often elevated.

Generally, neuropathies associated with MGUS respond less well to immunosuppressive or immunomodulatory therapy than idiopathic CIDP. IgG and IgA MGUS neuropathies respond better than IgM MGUS neuropathies to plasmapheresis. Improvement has also been documented with rituximab, fludarabine, and alkylating agents. Some patients have responded to IFN-α and IVIg. Long-term studies to determine the relationship between specific immunologic markers and disease recurrence will help to develop targeted therapies.

CRITICAL ILLNESS POLYNEUROPATHY

More than 50 percent of critically ill patients with sepsis and multiorgan disease fail to wean from ventilatory support. Examination in moderately advanced cases reveals flaccid, symmetric weakness, depressed or absent tendon reflexes, and impaired distal sensation. Other causes of weakness in the ICU setting include prolonged neuromuscular blockade from drugs, critical illness myopathy, and cervical myelopathy. CSF protein level is normal or only mildly elevated. Electrodiagnostic studies confirm the presence of a sensorimotor polyneuropathy. Treatment is supportive. The prognosis is variable, depending on the degree of axon loss. A more complete account of this disorder is provided in Chapter 56.

UREMIC NEUROPATHY

Uremic polyneuropathy presents as restless legs, weakness, cramps, and distal paresthesias and dysesthesias in patients with end-stage renal disease (serum creatinine levels of 5 mg/dL or higher). The prevalence among patients undergoing hemodialysis treatment is 50 to 60 percent. Electrodiagnostic studies typically show evidence of distal axon loss with some evidence of demyelination. Usually the neuropathy is slowly progressive, but rapidly progressive uremic neuropathy with prominent demyelinating features has been described. Renal transplantation is the best treatment for uremic polyneuropathy. Further details are provided in Chapter 16.

NEOPLASTIC AND PARANEOPLASTIC NEUROPATHIES

Monoclonal Gammopathy

Multiple myeloma, Waldenström macroglobulinemia, osteosclerotic myeloma (POEMS syndrome of polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes), lymphoma, and leukemia are associated with a monoclonal gammopathy. Generally, symptoms and signs are similar to those of polyneuropathy related to an MGUS. Frequently, these neuropathies are associated with significant distal weakness and some demyelinating features on NCSs.

Amyloidosis

Amyloidosis causes a slowly progressive distal sensorimotor polyneuropathy. Distal lower-extremity pain and paresthesias are common presenting symptoms. On examination, there is usually greater impairment of small- than large-fiber sensory function. Autonomic neuropathy frequently occurs, leading to orthostatic lightheadedness, diarrhea, bladder dysfunction, and impotence. CTS is also common.

In primary amyloidosis, the amyloid fibrils consist of portions of monoclonal immunoglobulin light chains (Bence Jones protein). In almost all these patients, a monoclonal protein may be detected in either the serum or urine. Diagnosis depends on identifying amyloid deposition in tissues. An abdominal fat aspirate is probably the best initial step for establishing the diagnosis; the diagnostic yield is more than 70 percent. If this is negative, a rectal or nerve biopsy may be considered. By suppressing monoclonal light-chain production, alkylating agents extend survival in patients with primary amyloidosis. Autologous peripheral blood stem-cell transplantation is also available, but has a high morbidity and mortality. In familial amyloidosis, the fibrils are usually composed of mutant transthyretin. Molecular genetic testing for transthyretin (TTR) mutations is a sensitive diagnostic test. Sometimes wild-type TTR can form amyloid deposits and also lead to neuropathy. TTR stabilizers (tafamadis and diflunisal) slow the progression of the disease. In addition, TTR antisense oligonucleotide (inotersen) and RNA interference (patisiran) therapies have been approved by the FDA for treatment of TTR amyloid polyneuropathy.[6,7] Orthotopic liver transplantation is an effective treatment for younger patients with amyloid polyneuropathy and the common TTR Val30Met mutation; outcomes for liver transplantation may be poor for other TTR mutations.

Paraneoplastic Neuropathy

Patients with anti-Hu (ANNA-1) antibodies usually present with a sensory neuropathy, but about 25 percent of patients present with a subacute sensorimotor polyneuropathy. Rarely, the associated neuropathy is acute, thereby mimicking GBS. Most of these patients have small cell lung carcinoma.

Peripheral neuropathy occurs as a feature of paraneoplastic syndromes associated with anti-CV2 antibody in about 50 percent of cases. Usually it is a mixed axonal and demyelinating sensorimotor polyneuropathy, but a pure sensory neuropathy may also occur. Rarely, sensorimotor neuropathies have been described with anti-Ri (ANNA-2) and anti-Yo (PCA-1) antibodies.

NUTRITIONAL NEUROPATHY

Vitamin B_1 (Thiamine) Deficiency

Thiamine deficiency is uncommon in industrialized countries. Inadequate consumption may occur in the context of chronic alcohol abuse, total parenteral nutrition, prolonged vomiting, and bariatric surgery. Initial neuropathic symptoms (dry beriberi) include burning dysesthesias in the feet with mild sensory loss. Fatigue, muscle aches, and cramps in the lower extremities are common. Although progression is usually subacute to chronic, the neuropathy sometimes develops over a few days. In severe cases, there may be significant weakness of ankle dorsiflexion and finger and wrist extension in addition to stocking-glove sensory deficits. The recurrent laryngeal nerve may become involved, causing hoarseness. With thiamine supplementation, the neuropathy typically improves, albeit modestly. Further details are provided in Chapter 15.

Vitamin B_6 (Pyridoxine) Deficiency

Deficiency of vitamin B_6 (pyridoxine) causes a distal axonal sensorimotor polyneuropathy. It is a known complication of taking the prescription medications isoniazid and hydralazine. If these medications are prescribed, oral supplementation of vitamin B_6 at daily doses of 50 to 100 mg is advised. Vitamin B_6 deficiency may also occur with chronic peritoneal dialysis or alcoholism.

Overdosing with vitamin B_6 may cause an ataxic sensory neuronopathy associated with degeneration of posterior root ganglia neurons. Stretch reflexes are hypoactive or globally absent. Most patients have numbness, paresthesia, and gait ataxia. Daily ingestion of as little as 200 mg per day has been associated with the development of a peripheral neuropathy in some instances.

Vitamin B_{12} (Cobalamin) Deficiency

The classic neurologic presentation of vitamin B_{12} deficiency is combined degeneration of the dorsal and lateral columns of the spinal cord. Patients present with distal numbness, paresthesias, and, occasionally, dysesthesias. Compared with patients with idiopathic distal polyneuropathy, patients with vitamin B_{12} deficiency are more likely to have concomitant involvement of the upper and lower extremities, initial symptom onset in the hands, and a sudden onset of symptoms. In more advanced cases, paraparesis occurs with extensor plantar responses. Malabsorption is the cause of most cases; it may be due to pernicious anemia, gastric or bowel surgery, or inflammatory bowel disease. Neurologic manifestations of vitamin B_{12} deficiency may occur without anemia or elevated mean corpuscular volume. Testing for elevations of serum homocysteine and methylmalonic acid is helpful when the vitamin B_{12} level is borderline low. With early treatment, the paresthesias may improve, but loss of large-fiber sensory axons is often permanent. Traditionally, vitamin B_{12} is supplemented with weekly to monthly intramuscular injections. Because individuals with pernicious anemia still absorb small amounts of vitamin B_{12}, oral supplementation at a dose of 1,000 to 2,000 μg daily may be equally effective.

Vitamin E Deficiency

Vitamin E deficiency presents as a spinocerebellar ataxia with polyneuropathy. It usually results from lipid malabsorption; errors of vitamin E absorption or transport are less common causes. Pathologically, there is degeneration of sensory axons, posterior root ganglia, posterior columns, and spinocerebellar tracts. The diagnosis is made by measuring serum α-tocopherol levels. Proper supplementation depends on the underlying cause of the deficiency.

Copper Deficiency

Copper deficiency has been associated with a myeloneuropathy characterized clinically by limb paresthesia and spastic paraparesis. Patients have deficits of large-fiber sensation, and many have extensor plantar responses. Often patients have microcytic anemia and neutropenia. Many patients have had prior gastric surgery. Some cases have been linked to excessive zinc levels, which are known to cause copper deficiency. Following copper supplementation, some patients show neurologic improvement.

TOXIC NEUROPATHY

Alcoholic Neuropathy

A distal axonal polyneuropathy is a common complication of chronic alcoholism, occurring in approximately 10 to 50 percent of patients, depending on the study and diagnostic criteria. Superficial sensation is principally impaired and dysesthesias are common. Pathologically, there is loss of sensory and motor axons. The pathophysiology is not fully understood but may involve direct toxicity of alcohol on peripheral nerves; vitamin deficiencies, including thiamine deficiency, are probable contributing factors. Treatment involves abstinence and vitamin supplementation. Prognosis is good for mild to moderate neuropathy after 3 to 5 years of abstinence. Further details are provided in Chapter 33.

Neuropathies Associated With Heavy Metal Exposure

Severe lead poisoning produces a subacute, asymmetric, predominantly motor neuropathy that preferentially affects the wrist and finger extensors. Footdrop is another common manifestation. Prognosis for recovery is good if the lead exposure is eliminated. Abdominal pain, anemia, encephalopathy, and mild sensory deficits may also occur.

Arsenic ingestion typically causes acute abdominal pain followed in 5 to 10 days by dysesthesias in the hands and feet. This is followed by an axonal polyneuropathy presenting as symmetric ascending weakness. The weakness may progress over several weeks. Recovery depends on the degree of axonal loss.

Additional details about the neurologic complications of heavy metal exposure are given in Chapter 35.

Medications and Other Chemicals

Medications and chemicals generally cause a subacutely progressive symmetric, distal, and length-dependent neuropathy, with sensory and motor axonal degeneration. A careful review of occupational exposures to toxins as well as exposures related to hobbies usually leads to candidate toxins. If the exposure is terminated, the neuropathy may continue to worsen for days to weeks (“coasting”) before its course is arrested. A number of toxins have been incriminated (Table 60-6 and Chapter 35).

HEREDITARY NEUROPATHY

Hereditary neuropathy typically presents with slowly progressive distal weakness and numbness. Examination of the feet may reveal pes cavus and hammertoes, features reflecting long-standing atrophy and weakness of the intrinsic foot muscles. Only those hereditary neuropathies with prominent systemic manifestations are discussed here.

Adrenomyeloneuropathy

Adrenomyeloneuropathy is a milder phenotype of adrenoleukodystrophy, the X-linked disease associated with degeneration of white matter and the adrenal cortex caused by mutations of the *ABCD1* gene. Adrenomyeloneuropathy may present from childhood to middle age, usually in men, but occasionally in women. Patients present with a spastic paraparesis, sphincter abnormalities, and sexual dysfunction with or without symptomatic adrenal insufficiency or cognitive problems. The neuropathy is responsible for weakness and depressed ankle reflexes. NCSs typically have shown a mixed axonal and demyelinating polyneuropathy. Testing for very-long-chain fatty acids is the initial diagnostic test for both males and females. Bone marrow transplantation is an effective treatment for those with MRI evidence of brain involvement and minimal neuropsychologic findings. Reduction of hexacosanoic acid by Lorenzo’s oil remains an investigational therapeutic approach for adrenoleukodystrophy.

Fabry Disease

Fabry disease is an X-linked recessive disorder of the gene encoding α-galactosidase A. Deficiency of this lysosomal enzyme causes widespread accumulation of globotriaosylceramide (GL-3) in cells throughout the body. Males present in adolescence with crises of severe pain in the extremities, vascular cutaneous lesions (angiokeratomas), hypohidrosis, corneal and lenticular opacities, and proteinuria. Renal function gradually deteriorates over time, leading to end-stage renal disease. In middle age, cardiovascular and cerebrovascular disease is another cause of significant morbidity and mortality. Patients have a distal small-fiber polyneuropathy with normal nerve conduction velocities. Pain may respond to phenytoin, carbamazepine, or gabapentin. The diagnosis is usually made by demonstration of deficient α-galactosidase A activity in plasma, leukocytes, or cultured cells. Hemodialysis or renal transplantation is often necessary. An expert panel has recommended that enzyme replacement therapy be initiated as early as possible for all males and for females with significant disease.

Porphyria

Inherited defects in the hepatic enzymes responsible for heme synthesis—the hepatic porphyrias—may be associated with acute episodes of CNS and peripheral nervous system dysfunction. These disorders include acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria. The erythropoietic porphyrias are associated with photosensitivity but not neurologic disease. Between attacks, patients with hepatic porphyrias are normal. An attack is typically triggered by a drug that activates the hepatic cytochrome P-450 system, although hypoglycemia and hormonal factors may also contribute.

Clinically, patients present with acute, severe colicky abdominal pain accompanied by psychiatric disturbances. Often, medications used to treat pain and anxiety only exacerbate the attack by inducing certain hepatic enzymes. A painful, often asymmetric axonal neuropathy typically appears 2 to 3 days after the onset of abdominal pain. The weakness frequently begins in the upper extremities. Proximal or distal muscle groups may be involved. Reflexes are usually lost in proportion to weakness, unlike the early areflexia typically seen in GBS. Despite the pain, sensory deficits are usually mild and patchy. The combination of abdominal pain and neuropathy makes the clinical presentation similar to heavy metal intoxication.

Screening for the hepatic porphyrias involves an analysis of the heme precursors in urine. The results of the urinalysis may be normal in asymptomatic carriers. Treatment includes stopping all medications that could potentially exacerbate the attack and infusing heme. Although recovery from the psychiatric disturbances is typically rapid, recovery of the peripheral nerves depends on the severity and extent of the axon loss; ultimate recovery of the peripheral nervous system is generally good.

Refsum Disease

Refsum disease is an autosomal-recessive disorder characterized by anosmia, retinitis pigmentosa, deafness, ataxia, ichthyosis, and neuropathy. Symptoms may begin at any age. Over 90 percent of cases are associated with mutations of the phytanoyl-CoA hydroxylase gene; less than 10 percent are associated with mutations of the *PEX7* gene. The consequence of these mutations is a build-up of phytanic acid in various tissues. The presence of high levels of serum phytanic acid (>200 μmol/L) establishes the diagnosis. Phytanic acid deposition in Schwann cells and the endoneurial space leads to a distal, symmetric sensorimotor neuropathy. Reduction of phytanic acid concentrations by dietary restriction, plasmapheresis, or lipid apheresis improves ichthyosis, sensory neuropathy, and ataxia but may not benefit the retinitis pigmentosa, anosmia, and deafness.

Tangier Disease

Tangier disease is a rare autosomal-recessive disorder caused by mutations in both alleles of the adenosine triphosphate-binding cassette A1 gene (*ABCA1*). The protein deficiency causes decreased lipid removal from cells, widespread tissue accumulation of cholesteryl esters, and the absence of plasma high-density lipoproteins (HDLs). Absent HDLs with normal triglyceride level and the presence of enlarged orange tonsils differentiates Tangier disease from other lipoprotein disorders. Patients may develop corneal opacities or hypersplenism. Despite the HDL deficiency, atherosclerosis does not develop earlier than normal. Polyneuropathy may take one of three forms: asymmetric, relapsing-remitting sensorimotor mononeuropathies, usually associated with normal conduction velocities; symmetric, slowly progressive distal polyneuropathy; and a slowly progressive neuropathy affecting the face and upper limbs with distal hand weakness and facial diplegia and accompanied by dissociative sensory loss that may mimic the presentation of a syrinx. There is currently no specific treatment for Tangier disease.

NEUROMUSCULAR JUNCTION DISORDERS

In disorders of the neuromuscular junction (Table 60-10), patients present with weakness but not numbness. The congenital myasthenic syndromes are discussed elsewhere.

Botulism

Botulism is an acute paralytic illness caused by a toxin produced by *Clostridium* bacteria. Botulism results from (1) ingestion of the preformed toxin with absorption through the intestines, accounting for the vast majority of cases of adult food-borne botulism; (2) ingestion of clostridial spores that colonize the intestines and produce the toxin, accounting for virtually all forms of infant botulism and occurring rarely in adults with altered intestinal flora; or (3) infection of a wound, with local production and absorption of the toxin ("wound botulism"). Improperly preserved food is the most common cause of food-borne botulism. In California, wound botulism has become a recognized complication of intravenous "black tar" heroin use. Botulism may occur in rare instances among patients treated with botulinum toxin for dystonia or other movement disorders.

Adult food-borne botulism is characterized by rapidly progressive cranial nerve palsies, descending weakness, and autonomic dysfunction. The most common symptoms and signs include dysphagia, hypoactive gag reflex, dry mouth, diplopia, ptosis, extraocular movement abnormalities, fixed or dilated pupils, bulbar or limb weakness (especially proximally), constipation, nausea,

TABLE 60-10 ■ Disorders of the Neuromuscular Junction

- Botulism
- Congenital myasthenic syndromes
- Lambert–Eaton myasthenic syndrome
- Myasthenia gravis
- Medications
  - Anesthetics (e.g., ether, isoflurane, lidocaine, methoxyflurane, procaine, succinylcholine)
  - Antibiotics (e.g., aminoglycosides, ampicillin, fluoroquinolone, lincosamides, macrolides, polymyxins, tetracyclines)
  - Anticonvulsants (e.g., phenytoin, trimethadione)
  - Cardiac drugs (e.g., β-adrenergic blockers, bretylium, calcium-channel blockers, lidocaine, procainamide, quinidine, trimethaphan)
  - Hormones (e.g., adrenocorticotropic hormone, corticosteroids, thyroid hormone)
  - Psychiatric drugs (e.g., lithium, phenelzine, phenothiazines)
  - Rheumatoid arthritis drugs (e.g., chloroquine, D-penicillamine)
  - Other medications (e.g., anticholesterol drugs, anticholinesterase toxicity, any respiratory depressant, aprotinin, botulinum toxin, carnitine, checkpoint inhibitors, curare and its derivatives, ergonovine, aminoglycoside eyedrops, β-adrenergic blockers, corticosteroids, gadolinium, interferon-alpha and -beta, intravenous radiographic contrast media, methimazole, oxytocin, quinine, tetanus antitoxin)
- Electrolyte disturbances
  - Calcium
  - Magnesium
- Toxins (e.g., cocaine, carbamate insecticides, organophosphate insecticides, black widow spider venom, scorpion venom, snake venom, tick neurotoxin)

and vomiting. Stretch reflexes are usually hypoactive or absent but may be normal. Mental status, sensation, and CSF are usually normal. There is usually no response to edrophonium chloride (Tensilon). Atypical symptoms, signs, and ancillary test results are not uncommon and do not exclude the diagnosis. The symptoms and signs in infant botulism are similar to those in adults, with the additional features of hypotonia, poor suck, and failure to thrive. Symptoms usually begin 18 to 36 hours after ingestion of the spores and progress rapidly over 2 to 4 days; recovery begins within a few weeks.

Eight toxin types have been described (A, B, C1, C2, D, E, F, and G), but human botulism is associated only with types A, B, and E and, rarely, with F and G. In all forms of botulism, the toxin initially becomes disseminated via the systemic circulation before uptake by the terminals of peripheral cholinergic axons. Once the toxin is inside the nerve terminals, essential proteins for acetylcholine (ACh) release are cleaved. Subsequently, both muscarinic and nicotinic nerve terminals degenerate. Recovery from botulism, therefore, requires regrowth of axon terminals and restoration of the neuromuscular junction.

The diagnosis of botulism is usually confirmed by the detection of the toxin in the serum, stool, or wound. In addition, the wound and stool specimens are cultured to identify the offending organism. Electrodiagnostic studies are also helpful in showing impaired neuromuscular transmission.

Treatment consists of early antitoxin administration and supportive care. For adults, an equine trivalent antitoxin is effective against the type A, B, and E toxins. An effective human antitoxin (BabyBIG) is available specifically for infants and has a much lower risk of anaphylaxis than the equine product.

Wound debridement and antibiotics are indicated for wound botulism but should probably be delayed until the antitoxin is given. Prognosis is usually excellent with proper supportive and respiratory care. Recovery may take several weeks to months, depending on the degree of nerve end-terminal destruction.

Lambert–Eaton Myasthenic Syndrome

Lambert–Eaton myasthenic syndrome (LEMS) is an autoimmune disorder in which antibodies directed against presynaptic voltage-gated calcium channels cause proximal limb and trunk weakness. Significant ptosis and bulbar weakness are uncommon. A striking clinical feature of LEMS is that strength often improves following brief exertion. Autonomic symptoms such as a dry mouth, constipation, and urinary retention are frequent. Tendon reflexes are usually hypoactive or absent but may improve after brief exercise.

Approximately 50 to 60 percent of patients with LEMS have an associated small cell lung cancer. Approximately 3 percent of patients with small cell lung cancer develop LEMS. Nonparaneoplastic LEMS also occurs, particularly in younger individuals.

Marked post-tetanic facilitation of the compound muscle action potential establishes the diagnosis. Detecting the presence of calcium-channel antibodies also confirms the diagnosis.

Survival in paraneoplastic LEMS depends on the treatment of the underlying neoplasm. Anticholinesterase drugs alone may modestly benefit strength. The drug 3,4-diaminopyridine is more effective; it works by blocking potassium channels, thereby prolonging the activation of voltage-gated calcium channels. The increased concentrations of calcium in the axon terminals facilitate ACh release presynaptically. Other treatments that may be effective include plasmapheresis, IVIg, prednisone, and azathioprine.

Myasthenia Gravis

There are two clinical forms of myasthenia gravis: ocular and generalized. In the ocular form, weakness is restricted to the eyelids and extraocular muscles. Individuals with generalized myasthenia frequently also have weakness of those muscles plus variable weakness of bulbar, respiratory, or limb muscles.

About 50 percent of patients present with ptosis or diplopia. Of these, about half will progress to generalized myasthenia gravis. A number of autoimmune diseases may be associated, including autoimmune thyroid disease and, more rarely, rheumatoid arthritis and systemic lupus erythematosus (SLE).

Approximately 75 percent of myasthenics have thymic abnormalities. Thymic hyperplasia is the most common abnormality; about 15 percent of patients have a thymoma, usually a noninvasive cortical thymoma. Approximately one-third of patients with a thymoma develop myasthenia gravis. Because of the risks of thymoma, MRI or CT of the mediastinum is necessary for all newly diagnosed myasthenic patients. Thymectomy is generally recommended for all patients with thymomatous myasthenia gravis. In rare instances, myasthenia gravis has been associated with small cell lung cancer and Hodgkin disease. Rarely, a medication such as D-penicillamine can induce the onset of autoimmune myasthenia gravis, possibly through antigenic mimicry.

The diagnosis is made by the history, examination, presence of ACh receptor antibodies (present in up to 90% of cases of generalized disease), edrophonium chloride test, and electrophysiologic studies. Approximately 35 to 50 percent of patients testing negative for ACh receptor antibodies have antibodies to LRP4 or muscle-specific receptor tyrosine kinase (MuSK). It is rare for patients to be positive to more than one of these antibodies. Patients with LRP4 antibodies do not have a distinct MG phenotype.[8] Most patients with MuSK antibodies are women, and many have prominent bulbar, neck, and respiratory weakness. Repetitive nerve stimulation testing for myasthenia gravis may be normal or only mildly abnormal in patients with MuSK-seropositive myasthenia. Treatment of myasthenia gravis consists of anticholinesterases, immunomodulation, thymectomy, or some combination of these approaches. A major prospective, multicenter trial has shown the benefit of thymectomy for seropositive, nonthymomatous generalized myasthenia gravis.

Medications and Toxins

A number of medications (Chapter 32) and toxins impair neuromuscular transmission. These are summarized in Table 60-10.

MYOPATHY

Myopathies usually present with symmetric, proximal weakness. Involvement of the neck flexors and extensors and the facial muscles is not uncommon, but weakness of the extraocular muscles is rare. Muscle atrophy and depressed stretch reflexes occur in advanced cases. The common causes of myopathy are listed in Table 60-11. The congenital and genetic myopathies are beyond the scope of this discussion and are covered in general neurology textbooks. Although myalgia may occur with certain myopathies, most myopathies (including the inflammatory myopathies) are painless. Exercise intolerance and exercise-induced muscle cramps are clues to one of the metabolic myopathies.

The evaluation for a suspected myopathy begins with measurement of serum creatine kinase (CK) activity. Increased serum CK levels usually imply sarcolemmal injury. Normal serum CK levels may occur with disuse atrophy, corticosteroid myopathy, mitochondrial myopathies, and critical illness myopathy associated with thick-filament loss. Many of the metabolic myopathies are associated with normal serum CK levels between attacks. Mild to moderate serum elevations of CK are generally seen with the inflammatory myopathies, toxic myopathies, and adult-onset muscular dystrophies. High serum CK levels are associated with severe toxic/necrotizing myopathies (related to medications or severe electrolyte disturbances) and muscular dystrophy presenting in childhood. Needle EMG supports the clinical diagnosis and excludes the possibility of a neuropathy. The electromyographer may also advise the best target for a muscle biopsy, which is often required for a definitive diagnosis.

TABLE 60-11 ■ Acquired Myopathies

Endocrine
- Acromegaly
- Corticosteroids
- Hyperparathyroidism
- Hyperthyroidism
- Hypothyroidism

Infectious
- Cysticercosis
- Human immunodeficiency virus
- Toxoplasmosis
- Trichinosis
- Viral myositis (e.g., adenovirus, influenza)

Inflammatory
- Dermatomyositis
- Inclusion-body myositis
- Polymyositis
- Polymyositis or dermatomyositis associated with
  - Scleroderma
  - Mixed connective tissue disease
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Sjögren syndrome
  - Systemic vasculitis
- Sarcoidosis

Medication-Related
- Chloroquine
- Colchicine
- Corticosteroids (see endocrine causes)
- Fibric acid derivatives (clofibrate, gemfibrozil, and others)
- 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (lovastatin, simvastatin, and others)
- Malignant hyperthermia (usually from general anesthetics)
- Vincristine
- Zidovudine

Metabolic and Toxic
- Alcohol
- Critical illness
- Hyperkalemia
- Hypokalemia
- Uremia

Endocrine-Related Myopathy

ACROMEGALY

Slowly progressive proximal weakness not associated with muscle atrophy occurs in about half of acromegalic patients. Many patients have decreased exercise tolerance. Serum CK levels may be mildly elevated. When growth hormone levels normalize, the myopathy usually resolves.

CORTICOSTEROID MYOPATHY

Corticosteroid myopathy may occur with either excessive exogenous or endogenous corticosteroids and is characterized by the insidious onset of proximal limb weakness. Patients who develop weakness usually have other stigmata of long-term corticosteroid use, including a moon facies, suprascapular fat pad, and fragile skin. Old age and cancer are risk factors for corticosteroid myopathy. Myalgias may occur. Serum CK levels are typically normal.

The dose and duration of corticosteroid treatment associated with the development of a myopathy vary widely, but most patients have received therapy for at least 4 weeks. With high-dose corticosteroids, however, the weakness may occur within 2 weeks of starting therapy. The fluorinated corticosteroids, including triamcinolone, betamethasone, and dexamethasone, are particularly likely to cause myopathy. Pathologically, there is selective atrophy of the type 2, glycolytic muscle fibers without muscle degeneration or inflammation. The pathogenesis probably relates to impairment of muscle protein and carbohydrate metabolism. The goal of treatment is to lower the corticosteroid dose to as low a level as possible. Recovery may take weeks to months but is usually excellent.

A severe, acute necrotizing myopathy can result from large doses of intravenous corticosteroids combined with a neuromuscular blocking agent, usually in the setting of treatment for status asthmaticus. There is probably overlap between this condition and critical illness myopathy (Chapter 56).

HYPERPARATHYROIDISM AND OSTEOMALACIA

Proximal muscle weakness may be associated with primary and secondary hyperparathyroidism, vitamin D deficiency, and other disorders of vitamin D metabolism.

Patients with primary hyperparathyroidism often complain of weakness and fatigue, but objective loss of muscle power is uncommon. Proximal weakness may be associated with discomfort on movement. Muscle stretch reflexes tend to be brisk. Serum CK levels are normal. Pathologically, atrophy of type II muscle fibers is a consistent feature. Secondary parathyroidism usually occurs in the setting of renal failure. The myopathy associated with uremia is discussed later.

Osteomalacia presents with proximal weakness and bone pain. Nutritional deficiency of vitamin D is the leading cause of osteomalacia worldwide, but gastrectomy and celiac sprue are responsible for most of the cases in the United States. Renal tubular acidosis and anticonvulsant therapy may also cause osteomalacia by interfering with vitamin D metabolic pathways. Vitamin D deficiency may lead to secondary hyperparathyroidism; it may then be difficult to determine which factor is more important in the pathogenesis of the weakness. When vitamin D—deficient patients are supplemented with vitamin D, the response is variable and any improvement occurs over many weeks.

HYPERTHYROIDISM AND HYPOTHYROIDISM

Approximately 50 percent of thyrotoxic patients develop weakness. The pattern of weakness is typically proximal; patients frequently complain of fatigue and breathlessness. Myalgia is common. Usually the onset is insidious, although the onset may be more rapid in severe hyperthyroidism. In fact, rhabdomyolysis with myoglobinuric renal failure may occur in the setting of a thyroid storm. In general, however, severe generalized weakness in thyrotoxic patients should raise the suspicion of concomitant myasthenia gravis. Serum CK levels are usually normal. The EMG reveals small, short, polyphasic motor units without abnormal spontaneous activity. In addition to nonspecific myopathic findings, muscle biopsies may reveal a lower proportion of type I fibers. Following treatment, the proportion of type I fibers increases. Prognosis for recovery is excellent once a euthyroid state is achieved.

Thyrotoxic periodic paralysis is characterized by recurrent attacks of generalized weakness lasting for minutes to days. The weakness may be provoked by a carbohydrate meal, cold, or rest after exercise. It is usually seen in young Asian or Native American adults. The paralytic attacks are not related to the duration or severity of the thyrotoxicosis. Treatment of acute paralytic attacks includes potassium supplements. The paralytic attacks disappear once the patient is maintained in a euthyroid state.

Hypothyroidism causes a myopathy characterized by proximal weakness, fatigue, slowed movements and reflexes, cramps, stiffness, myoedema, and muscle enlargement. The serum CK level is elevated even in asymptomatic hypothyroid patients and is frequently elevated more than 10 times the upper limit of normal in symptomatic patients. The EMG findings may be normal. Nonspecific myopathic findings are seen on muscle biopsy. After thyroid supplementation, recovery is excellent.

Infectious Myopathies

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

As discussed in Chapter 43, several different types of myopathy have been associated with HIV infection. First, an inflammatory myopathy resembling polymyositis (PM) both clinically and pathologically may occur. Although it may present at any stage of HIV infection, it is usually a complication of AIDS. Patients present with slowly progressive proximal arm and leg weakness. Serum CK levels are elevated, often more than 10 times the upper limit of normal. Pathologically, the findings are similar to idiopathic PM. Viral particles have not been identified in muscle cells. Most cases respond to corticosteroid therapy.

Second, a nemaline rod myopathy may occur with or without associated inflammation in HIV patients. Third, inclusion-body myositis (IBM) has been described in HIV patients. It is clinically and pathologically indistinguishable from sporadic IBM, except that the age at onset is earlier. Fourth, muscle atrophy and weakness occur in the HIV wasting syndrome. Pathologically, there is atrophy of the type II muscle fibers. Tumor necrosis factor α (TNF-α) is implicated in the pathogenesis of this syndrome. Fifth, myoglobinuria (sometimes recurrent) may occur at any stage of HIV infection. Multiple factors, including concomitant medication use, probably contribute to its pathogenesis. Sixth, a pyomyositis manifesting as localized pain and swelling in a limb may occur. It is usually associated with *Staphylococcus aureus* infection. Seventh, a proximal myopathy associated with myalgias in the thighs and calves may occur with high-dose zidovudine (AZT) treatment. Serum CK levels may be normal or mildly elevated. Pathologically, many fibers reveal "ragged red" features consistent with mitochondrial toxicity. Discontinuation of the medication usually results in improvement but sometimes not full recovery.

VIRAL MYOSITIS

Viruses implicated in causing a myopathy include adenovirus, coxsackievirus A and B, echovirus, influenza A and B, Epstein–Barr virus, adenovirus, echovirus, parvovirus, parainfluenza virus, paramyxovirus, CMV, hepatitis B, herpes simplex virus, herpes zoster, human T-lymphotropic virus 1 (HTLV-1), and HIV. Myalgia is the most common neuromuscular symptom associated with viral illness. After the viral illness, swollen muscles and sometimes rhabdomyolysis with myoglobinuria occur. For many of the virus strains mentioned here, there is no clear evidence that the virus actually infects or replicates within human muscle tissue. In such cases, the pathogenesis of the muscle injury is uncertain.

OTHER INFECTIONS

The three most common parasitic infections of muscle are toxoplasmosis, cysticercosis, and trichinosis.

Toxoplasmosis is the most common protozoan infection to cause a myositis, the others being sarcocystis, trypanosomiasis, microsporidiosis, and malaria. *Toxoplasma gondii* is transmitted to humans by ingestion of undercooked meats and by contact with cat feces. Patients present with a fever accompanied by any one of multiple possible systemic features, including lymphadenopathy, pericarditis, hepatosplenomegaly, meningoencephalitis, and myositis. The myositis associated with toxoplasmosis resembles idiopathic PM and dermatomyositis (DM). Pathologically, cysts containing bradyzoites may be seen in muscle fibers or near inflammatory infiltrates. Prognosis for a full recovery is excellent following treatment.

Cestode (tapeworm) infections resulting in myopathy include cysticercosis, echinococcosis, coenurosis, and sparganosis. Cysticercosis caused by *Taenia solium* infection may result from eating uncooked infected meat (particularly pork) and by the fecal–oral route. Patients may present with enlarged yet weak muscles (pseudohypertrophy). Myalgia and muscle tenderness are common.

Nematode (roundworm) infections associated with a myopathy include trichinosis, toxocariasis, cutaneous larva migrans, and dracontiasis. Trichinosis occurs after ingestion of inadequately cooked meat. Following a prodrome of abdominal cramps and diarrhea, patients develop generalized weakness that may be accompanied by the classic cutaneous stigmata of DM. Serum CK levels are elevated and eosinophilia is present.

Inflammatory Myopathies

DM, PM, and IBM present with subacute to chronic, symmetric proximal limb weakness with sparing of the ocular muscles. All share evidence of lymphocytic infiltration of the muscle, but important differences exist among these diseases, particularly in mechanisms of pathogenesis and response to treatment. Autoimmune necrotizing myopathies present in a similar fashion but lack lymphocytic infiltrates.

DERMATOMYOSITIS AND POLYMYOSITIS

The annual incidence of DM and PM in the general population is 0.1 to 1 per 100,000. Women are affected more often than men. Most patients present with a several-month history of subacute proximal weakness, usually without significant muscle atrophy. Typically, the onset of the weakness cannot be precisely recalled. Other symptoms may include dysphagia, nasal regurgitation, or aspiration from weakness of oropharyngeal muscles or the upper esophagus. Myalgias and muscle tenderness occur in 25 to 50 percent of cases but tend to be mild. Muscle pain is more prominent in viral or bacterial myositis, the inherited metabolic myopathies, polymyalgia rheumatica, and fibromyalgia.

In DM, various cutaneous manifestations may precede or accompany the onset of weakness. These include Gottron sign (scaly, erythematous rash over the extensor surfaces of the metacarpophalangeal and interphalangeal joints; a similar rash may occur over the extensor surfaces of the elbows and knees), diffuse flat erythema in the anterior neck and chest and other sun-exposed areas, swelling and reddish violaceous discoloration of the upper eyelids (heliotrope rash), periungual erythema, dilated nail-bed capillary loops, and rough, cracked skin at the fingertips (so-called mechanic's hands). Of note, patients with DM and SLE often share the same 308A polymorphism of the TNF-α promoter region, which suggests that ultraviolet light-induced production of TNF-α may contribute to light sensitivity in both diseases.

Interstitial lung disease is an important complication of PM and DM. Particularly for PM, the presence of interstitial lung disease is associated with antibodies to the histidyl-transfer RNA (histidyl-tRNA) synthetase (anti-Jo-1). The lung disease may precede the myopathy or accompany it in 5 to 40 percent of patients with DM and PM and may present acutely with a nonproductive cough, dyspnea, hypoxemia, and lung infiltrates or chronically with dyspnea. Sometimes it is discovered in asymptomatic patients on screening chest radiographs. The presence of interstitial lung disease is a poor prognostic factor for long-term survival. Patients with DM and PM may have cardiac involvement, which may manifest as supraventricular arrhythmias, atrioventricular conduction blocks, and bundle branch block. Congestive heart failure has also been described.

Malignancies are seen in 6 to 45 percent of DM patients and in 0 to 28 percent of PM patients. A wide variety of cancers are associated with DM including ovarian, lung, pancreatic, stomach, and colorectal cancer, and non-Hodgkin lymphoma. Non-Hodgkin lymphoma and lung and bladder cancers have been associated with PM. Age-appropriate cancer screening tests should be performed in all patients; in those over age 65 years, CT scans of the chest, abdomen, and pelvis are recommended. Pelvic ultrasonography and transvaginal ultrasound are advocated by some experts. Full laboratory screening studies are also important.

PM and DM may overlap with scleroderma, SLE, and, rarely, rheumatoid arthritis and Sjögren syndrome. In scleroderma, a bland myopathy with mild to absent elevations of serum CK levels is common. In a few patients, severe proximal muscle weakness occurs with significant serum CK elevations. Overall, the incidence of myositis in scleroderma ranges from 5 to 17 percent. In North American patients, the anti-PM-Scl antibody is a marker for scleroderma-myositis. PM and DM also occur in association with SLE. The presence of autoantibodies against nuclear components helps distinguish a PM-SLE overlap syndrome from idiopathic PM. Serum CK levels are usually elevated in PM and DM and generally reflect the disease activity; levels are generally higher in PM than DM and may even be normal in active DM.

Serum antibody tests to nuclear and cytoplasmic components help support the clinical diagnosis of PM or DM, assist the diagnosis of overlap syndromes, and categorize subgroups of inflammatory myopathies. Muscle-specific antibodies have specific associations with HLA haplotypes and certain disease manifestations. These include antibodies to aminoacyl transfer RNA synthetases, components of the signal recognition particle (SRP), and nuclear helicase/adenosine triphosphatase Mi-2. About 50 to 75 percent of those with antibodies to cytoplasmic transfer RNA synthetases (including anti-Jo-1) have interstitial lung disease. Patients with anti-SRP antibodies often have acute-onset severe myositis without an associated rash or lung disease. Patients with anti-Mi-2 antibodies usually have a florid rash and an abrupt onset of weakness. Patients with anti-MDA5 antibodies may have amyopathic DM and interstitial lung disease.

MRI shows evidence of inflammation in muscles and subcutaneous fat, fibrosis, and calcification. Because MRI is noninvasive, it can be performed serially to assess disease progression and monitor response to treatment; it may also be used to identify a site for biopsy.

EMG typically reveals increased insertional activity and fibrillation potentials with myopathic (low-amplitude, short-duration, polyphasic) motor unit potentials. Ideally, a muscle biopsy should be performed on a superficial muscle with abnormal findings on EMG of the homologous contralateral muscle.

Pathologically, the inflammation in PM is perivascular, perimysial, and endomysial. There is no evidence of damage to the capillaries. There is invasion of non-necrotic muscle fibers ubiquitously expressing major histocompatibility complex (MHC)-1 by cytotoxic CD8$^+$ T cells. These findings support the hypothesis that the cytotoxic T cells recognize an antigen bound to MHC-1. The identity and origin of this putative antigen are not known. MHC-1 is normally not expressed on the surface of muscle fibers.

In DM, the inflammation is predominantly in the perivascular or interfascicular space and less so in the endomysium. The inflammatory infiltrate is primarily composed of B cells and CD4$^+$ T cells. Unlike PM, the immune attack appears to be primarily directed against the vascular endothelium. The sequence of events is thought to include antibody deposition on the endothelial cells, followed by complement activation, and, finally, membrane attack complex (MAC)–mediated microvascular injury. Chronic ischemia is thought to produce perifascicular atrophy, a hallmark pathologic feature of DM.

Corticosteroids are widely recognized as first-line treatment for PM. The typical daily dose is 1 to 1.5 mg/kg. This dose is continued until strength improves and then a careful, slow taper is started. A number of agents, including azathioprine, methotrexate, cyclosporine, tacrolimus, or mycophenolate mofetil, may be used concurrently or subsequently for a corticosteroid-sparing effect. Patients taking prednisone plus azathioprine have a better functional outcome and need a lower prednisone maintenance dose than those taking prednisone alone. For refractory cases of DM and PM, IVIg appears to be effective. Results from a large randomized controlled trial of rituximab in myositis failed to meet the primary endpoint. Antitumor necrosis factor agents have shown mixed results in small randomized clinical trials. Plasmapheresis did not show a benefit in a double-blind, placebo-controlled trial.

INCLUSION-BODY MYOSITIS

IBM is a slowly progressive, debilitating myopathy of unknown cause. It is the most common myopathy in patients older than 50 years. Early involvement of the finger flexors, wrist flexors, knee extensors, and ankle dorsiflexors is common. Dysphagia may occur, which may be treated with a cricopharyngeal myotomy. A wide variety of autoimmune diseases have been described in association with IBM. Hyporeflexia is common; some patients have clinical and electrodiagnostic evidence of a peripheral neuropathy.

The serum CK level can be normal or up to 10-fold above the upper limit of normal. The EMG findings are similar to those of DM and PM, except that long-duration motor unit potentials are commonly observed and do not exclude the diagnosis of IBM. Many patients with IBM have anti-NT5C1A antibodies, but obtaining a muscle biopsy is generally indicated to confirm the diagnosis.[9]

Pathologically, there is endomysial inflammation with a $CD8^+$ T-lymphocyte predominance, basophil-rimmed vacuoles with eosinophilic inclusions, and intracellular amyloid deposits detected by fluorescence microscopy of Congo red-stained sections or electron microscopy demonstrating 15- to 18-nm tubulofilaments. The vacuoles contain various products of muscle degradation including myeloid bodies, membrane fragments, and debris. In addition, numerous proteins also expressed in Alzheimer disease are found in muscle fibers. This has led to the notion that IBM is a degenerative disease associated with aging. There is generally no effective immunomodulating treatment, although individual patients have responded to corticosteroids, IVIg, and mycophenolate mofetil.

NECROTIZING AUTOIMMUNE MYOSITIS

Necrotizing myopathies are usually toxin-induced and resolve with removal of the toxin; rarely, they are immune mediated and chronic. Patients present with progressive, symmetric proximal muscle weakness of acute or subacute onset. Some patients have distal weakness, and many have dysphagia. Serum CK levels can be elevated markedly (over 20 times the upper limit of normal). The autoimmune disorder may be idiopathic or, rarely, relates to malignancies or use of statin drugs. Paraneoplastic necrotizing myopathy may occur with gastrointestinal tumors, small cell lung cancer, and breast cancer. Other patients with necrotizing autoimmune myositis, usually without malignancies, have antibodies to the signal recognition particle (anti-SRP antibodies). An endomysial microangiopathy leading to capillary loss occurs in anti-SRP myopathy. Rarely, statin drugs may cause a necrotizing autoimmune myositis that persists despite discontinuation of the drug. These patients usually have anti-HMGCR antibodies; some patients with autoimmune necrotizing myopathies associated with anti-HMGCR antibodies have never been exposed to a statin drug.

SARCOIDOSIS

Granulomatous inflammation of muscle is usually associated with sarcoidosis but can also be seen in infectious disease, inflammatory bowel disease, foreign body reactions, thymoma, lymphoma, and myasthenia gravis. It may also occur without any evidence of systemic disease.

Asymptomatic involvement of the muscle occurs in 50 to 80 percent of cases of sarcoidosis. Symptomatic involvement occurs in less than 3 percent of cases. Most patients with sarcoid myopathy present with slowly progressive, proximal weakness. Rarely, patients present with acute myositis or a palpable nodular type of myopathy. The response to corticosteroid therapy is unpredictable. Compared with sarcoid myopathy, patients with isolated granulomatous myopathy have milder, predominantly distal weakness, and the response to corticosteroids tends to be better.

POLYMYALGIA RHEUMATICA

Polymyalgia rheumatica presents with achiness and morning stiffness in the shoulder and hip girdles in patients older than 50 years. Malaise, fever, and anorexia with weight loss are common. There is an association with temporal arteritis and rheumatoid arthritis. The erythrocyte sedimentation rate is almost always increased. Despite functional limitations, confrontational motor testing is generally normal, as also is muscle biopsy. MRI or ultrasonography of the shoulders consistently reveals evidence of bursitis. The symptoms usually respond to low-dose corticosteroids.

Critical Illness Myopathy

Patients with critical illness may develop an acute, acquired myopathy associated with exposure to high-dose corticosteroids and neuromuscular blocking agents (Chapter 56). Critical illness myopathy may be suspected first when patients fail to wean from mechanical ventilation. Patients have flaccid, diffuse weakness that affects the limbs, neck flexors, and diaphragm. Tendon reflexes are usually depressed. Approximately one-third of ICU patients treated for status asthmaticus develop critical illness myopathy. Other risk factors include severe medical illness, renal failure, and hyperglycemia. Patients with critical illness myopathy may also have clinical and electrodiagnostic features of critical illness polyneuropathy. Critical illness myopathy should be distinguished from rhabdomyolysis with myoglobinuria, which can also occur in the ICU setting. Electrodiagnostic testing helps to clarify the diagnosis. Needle EMG reveals fibrillation potentials in limb muscles of some but not all patients. Short, small, polyphasic motor unit potentials are seen. Electrical inexcitability of the muscle to direct needle stimulation occurs in this entity but not in polyneuropathy. Most patients have elevations of serum CK levels, but a normal level does not exclude the diagnosis. Pathologically, there is muscle-fiber atrophy with evidence of a disrupted intramyofibrillar network. Loss of thick filaments (myosin) is a characteristic feature. The pathogenesis is uncertain but may involve glucocorticoid-induced proteolysis of contractile proteins in the setting of muscle-fiber denervation. There is no specific treatment for critical illness myopathy, but corticosteroids and neuromuscular blocking agents should be limited, if possible. Neurologic recovery is usually excellent, assuming that the patient recovers from the underlying medical illness.

Metabolic and Toxic Myopathies

ALCOHOL

Alcoholics may develop an acute necrotizing or chronic myopathy. The acute form presents as an attack of pain and swelling in a limb, usually the calf or thigh. In severe cases, myoglobinuria occurs. The attack usually occurs in the course of a heavy drinking binge. If probed, patients may recall prior bouts of pain and swelling in the limbs associated with earlier drinking binges. Serum CK levels are often markedly elevated. Recovery usually occurs over 1 to 2 weeks, but patients are prone to have subsequent episodes of acute myopathy if drinking is resumed.

The chronic form presents as chronic limb-girdle weakness with preserved reflexes. Serum CK levels are usually normal but may be elevated. Muscle biopsy specimen abnormalities are usually mild and include type II fiber atrophy.

HYPERKALEMIA OR HYPOKALEMIA

Hyperkalemia causes acute generalized weakness and cardiac arrhythmias. The weakness typically begins in the legs and then generalizes over hours to days. Respiratory failure occurs in about 50 percent of cases. Painful dysesthesias may precede the onset of weakness. Reflexes are usually absent. In most cases, the serum potassium level exceeds 7.5 mEq/L. Paralysis only occurs in patients with some degree of chronic hyperkalemia. Electrodiagnostic testing has shown slowing of nerve conduction velocities and low compound muscle action potential amplitudes. The immediate treatment goal is to prevent a cardiac arrhythmia, which can be achieved with an infusion of calcium gluconate.

Hypokalemia may be associated with acute paralysis or subacute myopathy. Acute hypokalemic paralysis occurs in patients with chronic potassium depletion. The onset of weakness occurs over hours to days. Once it starts, the weakness tends to accelerate. In mild cases, weakness may be limited to the legs, but in severe cases quadriplegia with neuromuscular respiratory failure may occur. Extraocular muscles are spared. The potassium level is always below 3.0 mEq/L. The subacute myopathy associated with hypokalemia is characterized by the onset of proximal limb weakness over weeks to months. Serum CK levels are elevated, sometimes markedly. Pathologically, there is muscle-fiber necrosis with multiple vacuoles in some muscle fibers. Occasionally, the course may be more rapid, associated with myalgia, tenderness, and myoglobinuria. Once the hypokalemia is corrected, recovery is rapid and complete.

UREMIA

Uremic myopathy, characterized by proximal weakness, limited endurance, and rapid fatigability, occurs in patients with end-stage renal disease. It usually only occurs with glomerular filtration rates below 25 mL/min. Approximately 50 percent of dialysis patients have this condition. Often, the weakness is mild, and EMG and serum CK levels are normal. Pathologically, there is atrophy of type II muscle fibers. A number of metabolic derangements may contribute to this condition, including secondary hyperparathyroidism, impaired vitamin D metabolism, carnitine deficiency, and reduced clearance of toxic "middle molecules." Insulin resistance, alterations of mitochondrial metabolism, and anemia may also have roles in pathogenesis. Although there is currently no specific treatment for uremic myopathy, an emphasis should be placed on preventing secondary hyperparathyroidism and improving the patient's nutritional status. Carnitine supplementation may be considered. Renal transplantation offers the best chance of improvement.

Medication-Induced Myopathy

Many different medications cause a myopathy (Chapter 32). Most of these cause a necrotizing myopathy that presents clinically with the acute to subacute onset of generalized weakness. In severe cases, myoglobinuria occurs. Myalgias may occur. Serum CK values are usually elevated. Pathologically, necrosis and regeneration of muscle fibers occur, with myophagocytosis. Statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors), fibric acid derivatives (clofibrate, gemfibrozil, and others), organophosphates, α-aminocaproic acid, and hypervitaminosis E are all associated with a necrotizing myopathy. Any medication that lowers potassium levels, including diuretics, licorice, and laxatives, may produce a myopathy. Chronic hydroxychloroquine or colchicine use can cause vacuolar myopathy; impaired renal function significantly increases the risk of colchicine-induced myopathy. A few medications (e.g., zidovudine) cause a mitochondrial myopathy. Once the offending medication is discontinued, most patients make a rapid and full recovery.

Statin-Induced Myopathy

Statins rarely cause a necrotizing myopathy with hyper-CKemia. In most patients, the myopathy reverses in weeks to months after withdrawal of the statin, and the serum CK levels normalize. In a subset of patients, however, the myopathy persists despite drug discontinuation. Evidence for an autoimmune basis for this myopathy includes: (1) expression of MHC-1 antigen on non-necrotic muscle fibers, (2) the presence of autoantibodies against muscle 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), and (3) improvement with immunosuppressive therapies such as prednisone. High levels of HMGCR in regenerating muscle fibers may be responsible for triggering or perpetuating the immune response.

RHABDOMYOLYSIS AND MYOGLOBINURIA

Any cause of muscle injury leads to an increase in serum concentration of myoglobin. Urine dipstick tests are positive when urine concentrations of myoglobin reach 0.5 to 1 mg/dL. If the concentration of myoglobin in the urine surpasses 250 μg (normal is less than 5 ng/mL), the urine will have a cola-color tinge. This reflects destruction of more than 100 g of muscle.

Recognition of myoglobinuria is important because of the potentially life-threatening complication of acute

TABLE 60-12 ■ Acquired Causes of Myoglobinuria and Rhabdomyolysis

Trauma or Infarction

Compartment syndromes
Crush injuries
Immobilization

Infections

Viral
- Adenovirus influenza A and B
- Coxsackievirus
- Cytomegalovirus
- Enterovirus
- Epstein–Barr virus
- Herpes simplex virus
- HIV
- Varicella-zoster

Bacterial
- *Francisella tularensis*
- *Clostridium*
- *Legionella*
- *Leptospira*
- *Neisseria*
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Salmonella typhi*

Nontraumatic Overexertion

Exercise
Prolonged dystonia or chorea
Delirium
Status epilepticus

Extremes of Body Temperature

Burns
Fevers
Hypothermia

Drugs and Toxins

Drugs
- Antidepressants (all classes)
- Depolarizing neuromuscular blockers (succinylcholine)
- HMG-CoA reductase inhibitors
- Inhaled anesthetics (halothane)
- Neuroleptic medications
- Nonsteroidals
- Miscellaneous
  - Azathioprine
  - Colchicine
  - Gemfibrozil
  - Pentamidine
  - Pyrazinamide
  - Zidovudine

Toxins
- Amphetamines
- Arsenic
- Carbon monoxide
- Cocaine
- Ecstasy
- Ethanol
- Ethylene glycol
- Haff disease
- Strychnine
- Venoms (bee, hornet, snake, spider, and parrotfish)

Metabolic Abnormalities

Diabetic ketoacidosis
Hypokalemia
Hyper- or hyponatremia
Hypophosphatemia
Hypothyroidism

Inflammatory Myopathy

Dermatomyositis
Polymyositis

tubular necrosis. Management includes hydration with alkaline fluids and induced diuresis with hyperosmolar agents such as mannitol. Electrolyte imbalances, such as hyperkalemia or hypocalcemia, may cause cardiac arrhythmias and require prompt reversal. The prognosis for neurologic recovery is usually excellent given the tremendous regenerative capacity of skeletal muscle.

Rhabdomyolysis leading to myoglobinuria may occur when there is direct injury to the sarcolemma or when energy failure occurs. In addition to pigmenturia, presenting symptoms include myalgia, weakness, and muscle swelling. The many causes of myoglobinuria are outlined in Table 60-12.

It should be noted that vigorous exercise (e.g., military physical fitness training) elevates serum CK values in most people (commonly exceeding five times the upper limit of normal), but visible myoglobinuria or muscle weakness is rare. Polymorphisms in the myosin light-chain kinase, α-actin 3, and creatine kinase MM genes have all been associated with higher serum CK elevations after exercise and may be risk factors for exertional myoglobinuria.

Recurrent myoglobinuria, regardless of whether it is associated with exercise, should prompt an investigation into a metabolic myopathy. Glycogen storage diseases, fatty acid oxidation disorders, and mitochondrial cytopathies have all been associated with recurrent myoglobinuria. Diagnosis of these disorders usually requires the analysis of specific enzyme activities in muscle biopsies.

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CHAPTER

61

Disorders of Consciousness in Systemic Diseases

J. CLAUDE HEMPHILL

CONSCIOUSNESS
- Historical Perspective
- Definition of Consciousness
- Anatomy of Consciousness
- Implications for Systemic Diseases

MECHANISMS OF IMPAIRED CONSCIOUSNESS IN SPECIFIC DISEASES
- Metabolic Encephalopathies
- Systemic Disorders With Focal Neurologic Manifestations
- Systemic Diseases Presenting as Primary Neurologic Disorders

APPROACH TO PATIENTS WITH DISORDERED CONSCIOUSNESS
- Neurologic History and Examination
- Neuroimaging
- Electrophysiologic Studies
- Cerebrospinal Fluid and Other Laboratory Studies
- Diagnosis and Treatment: Coordinated Clinical Approach

PROGNOSIS

BRAIN DEATH

VEGETATIVE AND MINIMALLY CONSCIOUS STATES

Consciousness is a complex and elusive concept that has been the subject of extensive thought and speculation by philosophers, theologians, and scientists since antiquity. The fact that consciousness may mean different things depending on the context (philosophy, religion, science) demonstrates the importance that understanding normal and disordered consciousness holds across a wide variety of fields of study. In medicine, disorders of consciousness are pervasive among the effects of systemic diseases on the nervous system. Because alterations in consciousness may have important diagnostic, therapeutic, and prognostic implications, a pragmatic approach using the neurologic principle of localization and the medical approach of differential diagnosis is useful. The spectrum of consciousness, from wakefulness to coma to brain death, has an anatomic and biologic substrate.

CONSCIOUSNESS

Historical Perspective

Ever since the Greek physician Galen (130 to 200 A.D.) recognized that a wound of the brain could affect the mind, the roles of consciousness and thought as manifestations of brain injury and impairment have held a special role. During the Renaissance, the philosopher Descartes (1596 to 1650) focused on the "mind–brain problem." He thought that the pineal gland was the seat of the soul, and this structure therefore played a special role in his concept of consciousness, although contemporaries granted this honor to the corpus callosum. Late nineteenth and early twentieth century efforts such as William James's "stream of consciousness" focused on psychologic, not anatomic, mechanisms. Although the effect of systemic diseases on consciousness has been recognized since Hippocrates in the fifth century B.C. described "madness on account of bile," the ability to ascribe testable anatomic and biologic correlates to consciousness is distinctly modern. The two main advances that have made this possible are (1) development of an operational definition of consciousness that has practical applicability and (2) understanding of the anatomic substrate of consciousness.

Definition of Consciousness

In medicine, consciousness can be defined as awareness of self and the environment. Thus, decreased consciousness involves impairment of this state of awareness, with coma being its absence. Consciousness

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TABLE 61-1 ■ Spectrum and Components of Consciousness

Spectrum of Arousal
Alert
Confused
Lethargic
Obtunded
Stuporous
Comatose
Components of Content
Cognition (thought)
Awareness of environment
Memory
Language
Visuospatial integration

and conscious behavior have two basic components: arousal and content. Arousal is behaviorally related to the level of alertness or wakefulness. Content describes the complex range of cognitive functions, including thought, memory, and language. As described later, a simplified anatomic model of consciousness gives arousal and content distinct anatomic localizations. Arousal and content may be independent but are frequently interdependent. For content to be present or at least to be assessed clinically, some degree of arousal must be present. Conversely, if decreased arousal (e.g., from sedative drug intoxication) is overcome by a noxious stimulus, content may be seen to be largely normal until arousal fades again. A description of the state of consciousness of an individual must take into account both level of arousal and quality of content. Different diseases and neuroanatomic sites may be implicated, depending on the specifics of the state of consciousness. The term *level of consciousness* usually refers to level of arousal (Table 61-1).

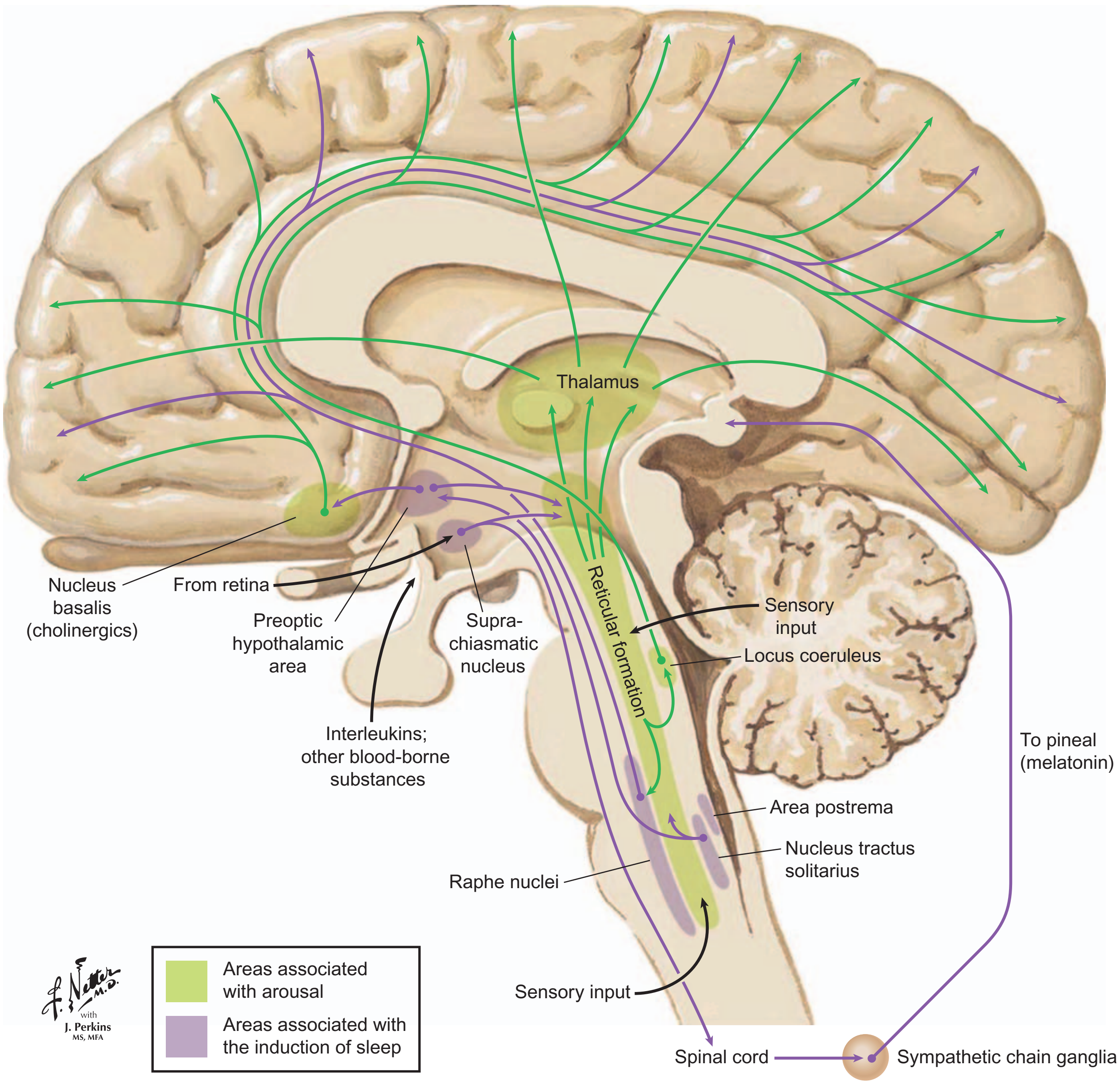
Anatomy of Consciousness

Although somewhat of an oversimplification, the two different components of consciousness are mediated by two distinct neuroanatomic systems (Fig. 61-1). Arousal is mediated by the ascending reticular activating system (RAS). The RAS is located in the brainstem and is a loosely arranged column of neurons extending from the upper third of the pons to the diencephalic structures of the thalamus and hypothalamus.[1] Projections via subcortical relay nuclei, primarily in the thalamus, integrate RAS-mediated arousal with more diffuse cerebral cortical functions. Experimental studies have demonstrated that stimulation of the RAS in a sleeping animal results in immediate behavioral arousal, but when the RAS is destroyed, no amount of sensory stimulation reverses coma, even with subcortical and cortical structures intact.

The content of consciousness is localized more broadly throughout the cerebral cortex. Certain cognitive functions are diffusely localized throughout both cerebral hemispheres, whereas other functions may have more narrow localization. Receptive language and expressive language are principally localized to the superior temporal lobe or posterior frontal lobe, respectively, of the dominant hemisphere. Although various aspects of memory may be stored diffusely, the mesial temporal lobes and mammillary bodies are important for storage of new short-term memory. Conversely, processes such as thought, orientation, attention, and planning are localized diffusely, especially among both frontal lobes. Because a severe impairment of receptive language is likely to alter the state of awareness of self or environment (as far as can be deduced by examination), some may consider it an altered state of consciousness. Others place more emphasis on impairment of bihemispheric dysfunction, evidenced by decreased attention, concentration, and coherent thought, as defining altered content of consciousness. The important lesson is that different aspects of the content of consciousness may have different anatomic localizations and that global impairment of cognitive function implies bilateral cerebral hemispheric dysfunction or disease.

Implications for Systemic Diseases

Coma, or unconsciousness, is a state of unresponsiveness in which the subject has closed eyes and cannot be aroused appropriately with stimuli. For coma to be present, one of two general anatomic conditions must be satisfied: there must be significant impairment of either the RAS or both cerebral hemispheres (Table 61-2). Structural lesions usually cause coma through direct brainstem involvement or through brainstem displacement or compression with subsequent RAS involvement. The underlying pathologic processes are often primary neurologic disorders such as intracerebral hemorrhage, traumatic brain injury, subdural hematoma, brain tumors or


Thalamus
Nucleus basalis (cholinergics)
From retina
Preoptic hypothalamic area
Supra-chiasmatic nucleus
Interleukins; other blood-borne substances
Reticular formation
Sensory input
Locus coeruleus
To pineal (melatonin)
Area postrema
Nucleus tractus solitarius
Raphe nuclei
Sensory input
Spinal cord
Sympathetic chain ganglia
🟩 Areas associated with arousal
▨ Areas associated with the induction of sleep
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with
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FIGURE 61-1 ■ Neuroanatomy of consciousness. The reticular formation [also known as the reticular activating system (RAS)] is a loosely arranged column of neurons located in the brainstem. Arousal is largely mediated by the RAS through projections to the cerebral cortex through the thalamus. The content of consciousness is localized more diffusely throughout the cerebral cortex. The reticular formation is distinguished from other brain structures associated with induction of sleep. (From Felten DL, Jozefowicz R: Chapter 11. Brain stem and cerebellum. p. 172. In Neuroscience - Felten 1E, Netter Image ID: 8534.)

abscesses, or large cerebral infarctions with mass effect. Transtentorial herniation because of a supratentorial mass, direct brainstem impingement from an infratentorial lesion, or direct parenchymal brainstem involvement from hemorrhagic or ischemic stroke are common examples. Less commonly, subfalcine herniation or bihemispheric mass lesions may lead to coma with an intact brainstem due to diencephalic injury. Metabolic disturbances, by contrast, usually cause coma from diffuse bihemispheric involvement, which presumably results in disconnection between the RAS (and subcortical thalamic relay nuclei) and the hemispheres. The neurologic examination of the comatose patient is an important key in distinguishing the cause and anatomic basis of coma, specifically the presence or absence of brainstem and cranial nerve abnormalities such as pupillary or extraocular movement dysfunction. The cause of lesser degrees

TABLE 61-2 ■ Neuroanatomic Localization of Coma

Brainstem (RAS)

- Brainstem compression
  - Transtentorial herniation from supratentorial mass lesion
    - Subdural hematoma
    - Intracerebral hemorrhage
    - Post-traumatic cerebral edema
    - Large hemispheric infarction with mass effect
    - Brain tumor or abscess
    - Acute hydrocephalus
  - Infratentorial mass lesion
    - Cerebellar hematoma
    - Cerebellar infarct
    - Cerebellar tumor
- Intrinsic brainstem involvement
  - Pontine hemorrhage
  - Basilar artery occlusion
- Metabolic brainstem involvement
  - Severe hypoxic-ischemic injury
  - Anesthetic agents (?)
  - Severe organ failure (?)

Bilateral Cerebral Hemispheres

- Subfalcine (cingulate) herniation
  - Brain tumor or abscess (with edema)
  - Large hemispheric infarction with mass effect
- Bilateral structural hemispheric involvement
  - Widely metastatic cancer
  - Primary brain tumor (crossing corpus callosum)
- Metabolic encephalopathy
  - Organ failure
  - Medications (drugs)
  - Hypoxic-ischemic injury

RAS, reticular activating system.

of impaired level of consciousness can also be assessed by determining whether bihemispheric or brainstem dysfunction is responsible.

Sleep should be considered as a separate and distinct entity. Externally, patients in coma initially appear asleep, but sleeping individuals can be roused and then respond to the environment. Normal sleep has several stages that have distinct electroencephalographic (EEG) patterns as discussed in Chapter 51. The EEG findings in coma may vary, depending on the cause, but, in general, do not resemble those of sleep. Altered consciousness in systemic disease is a pathologic state in contrast to sleep, which is a necessary and normal function.

MECHANISMS OF IMPAIRED CONSCIOUSNESS IN SPECIFIC DISEASES

A practical approach to determining the cause of impaired consciousness in systemic disease requires an understanding of the mechanisms by which primary neurologic disorders as well as systemic diseases may affect the central nervous system (CNS). The neuroanatomic localization of consciousness implies that both focal and global, or diffuse, processes may alter the level or content of consciousness. Structural causes are intuitively easier to understand than many metabolic or diffuse causes. Compression, distortion, or infarction of the brainstem and RAS are processes for which urgent interventions, such as neurosurgical evacuation of a mass lesion or thrombectomy of an occluded artery, may be indicated. In contrast, metabolic encephalopathies cause impaired consciousness (either content or arousal) by interfering diffusely with the functions of the brain on a biochemical level; however, some metabolic encephalopathies can be considered "structural" on a microscopic level when they result in direct cellular brain injury. Although the mechanisms by which systemic diseases cause alteration in consciousness are diverse, they can be divided into three broad categories: metabolic encephalopathies, focal neurologic manifestations of systemic disorders, and primary neurologic disorders caused by systemic disease.

Metabolic Encephalopathies

Metabolic encephalopathy is the most frequent cause of disordered consciousness in systemic diseases and is defined as an alteration in consciousness caused by diffuse or global brain dysfunction from impaired cerebral metabolism. The list of metabolic encephalopathies is extensive and includes such disparate conditions as hypoxic-ischemic encephalopathy, hepatic encephalopathy, drug overdose, bacterial meningitis, and the postseizure state. The principal reason for grouping together this wide variety of disorders is that the neurologic examination may appear quite similar regardless of the underlying etiology. Nevertheless, the cause of the metabolic encephalopathy is the fundamental determinant of treatment and prognosis. Thus, considering the biochemistry of metabolic encephalopathies is of prime importance in their differentiation.

Two common themes emerge with regard to presumptive etiologies of metabolic encephalopathies in systemic disease: impaired substrate delivery (glucose or oxygen) to the brain or release by a systemic disease of a circulating substance that crosses the blood–brain barrier (or enters through a broken blood–brain barrier) and causes neuronal and cellular dysfunction (Table 61-3). The former, implicated in hypoxic-ischemic encephalopathy and hypoglycemia, may result in irreversible brain injury. The latter, implicated in most metabolic encephalopathies associated with organ system dysfunction (e.g., hepatic, renal) or with systemic infection, may be largely reversible if the underlying disorder is treated.[2] Although there are exceptions, this mechanistic differentiation can be of great importance in determining treatment and prognosis.

When substrate delivery to the brain is globally reduced, encephalopathy and eventually coma may result. Hypoxia, and especially hypoxia-ischemia, may result in permanent cerebral damage diffusely or in selectively vulnerable areas such as the hippocampus, cerebellum, and thalamus. The degree and duration of hypoxia or decreased cerebral blood flow determine the severity and irreversibility of damage. Hypoxic-ischemic encephalopathy most commonly results from severe hypotension or cardiac arrest and is mediated by the neuronal ischemic injury cascade, which includes release of excitatory amino acids, intracellular calcium influx, lipid peroxidation, and cell breakdown. Multiple clinical trials have demonstrated a beneficial effect of immediate treatment of severely neurologically impaired survivors of cardiac arrest with mild hypothermia (maintaining 33° to 36°C for 12 to 24 hours), and this treatment is part of standard resuscitation guidelines as discussed in Chapter 9.[3] Hypoglycemic encephalopathy is potentially reversible, but permanent damage may occur if it is not treated early. Hypertensive encephalopathy may be due to disordered cerebral autoregulation, elevated cerebral vascular resistance, and subsequent globally decreased cerebral blood flow. These substrate-delivery encephalopathies have altered cerebral oxygen and glucose delivery as a common pathway, regardless of cause, and may result in severe permanent neurologic damage if not treated urgently.

In contrast, systemic organ failure is a common cause of metabolic encephalopathy and carries a different prognosis than the substrate-delivery encephalopathies. Kidney (uremia) and liver failure are common causes. Carbon dioxide narcosis from pulmonary failure and, rarely, pancreatic failure can also cause encephalopathy. The biochemical mechanism of uremic encephalopathy is not known precisely, but decreased ability to utilize adenosine triphosphate by the uremic brain and elevated calcium content in the cerebral cortex and hypothalamus have been suggested. In hepatic encephalopathy, endogenous benzodiazepine-like substances may play a role, as suggested by animal studies and from experience in humans with improvement after administration of flumazenil. In hepatic failure,

TABLE 61-3 ■ Mechanisms of Metabolic Encephalopathies

Impaired Substrate Delivery
Hypoxia-ischemia
Hypoglycemia
Organ Failure
Hepatic encephalopathy
Renal failure
Pancreatic encephalopathy
Carbon dioxide narcosis
Circulating Cytokines (Putative)
Sepsis
Multisystem organ failure
Meningitis
Electrolyte Abnormalities
Hyponatremia
Hypernatremia
Hypercalcemia
Diffuse Brain Infection
HIV infection
Syphilis
Lyme disease
Autoantibodies
Paraneoplastic syndromes
Collagen vascular diseases
Diffusely Decreased Cerebral Metabolism
Medications/anesthesia/sedative drugs
Hypothermia

HIV, human immunodeficiency virus.

elevated levels of α-ketoglutaramate in the cerebrospinal fluid (CSF) correlate with systemic elevations in ammonia as well as depth of coma. Patients with fulminant hepatic failure may also have severe diffuse cerebral edema, and the acutely increased intracranial pressure provides a structural basis for the coma in this situation. Abnormal function of endocrine organs may cause encephalopathy through primary mechanisms (e.g., myxedema coma, thyrotoxicosis, hypocortisolemia) or through changes in electrolytes or the cerebral acid–base environment (e.g., hypercalcemia in hyperparathyroidism).

Encephalopathy frequently accompanies sepsis, especially when associated with multisystem organ failure. Critically ill patients may have multiple reasons for encephalopathy including primary organ failure (especially of kidneys and liver), electrolyte abnormalities, and concurrent use of sedative agents to facilitate interventions such as mechanical ventilation. However, sepsis itself is associated with a metabolic encephalopathy. Although proposed mechanisms of septic-associated encephalopathy range from multiple microabscesses throughout the brain to alterations in cerebral blood flow mediated by nitric oxide, circulating cytokines that cross the blood–brain barrier and are released during sepsis or the systemic inflammatory response syndrome are likely to be implicated. In contrast to substrate-delivery metabolic encephalopathies, these alterations in consciousness are generally thought to be largely reversible if the underlying organ pathologic process or sepsis is reversed.

Electrolyte and acid–base disturbances are common causes of encephalopathy. Among these, hyponatremia, hypernatremia, and hypercalcemia are most commonly associated with a decreased level of consciousness. In most circumstances, these encephalopathies are reversible, although rapid correction of hyponatremia should be avoided to decrease the potential of osmotic demyelination syndrome.

A global decrease in the cerebral metabolic rate of oxygen consumption may occur during profound hypothermia and following sedative drug overdose. This is reversible if substrate delivery is maintained. Thus, general anesthesia itself can be viewed as a cause of reversible metabolic encephalopathy or coma. Metabolic encephalopathy, often without a markedly decreased level of consciousness, may be caused by numerous prescription medications and may be mistaken for dementia in the elderly. Encephalopathy may also be a manifestation of collagen vascular disease (e.g., systemic lupus erythematosus, SLE), or systemic cancer. Although the latter may be mediated by electrolyte disturbances in the setting of the syndrome of inappropriate secretion of antidiuretic hormone or through paraneoplastic antibodies or circulating cytokines, these disorders may also cause alterations in consciousness from focal processes related specifically to the underlying cancer or collagen vascular disease.

The term *delirium* refers to a state of globally disturbed consciousness in which a subject has decreased attention and an altered sensorium, usually developing over hours to days and often with fluctuating symptoms. Agitation and hallucinations may be present but are not required for the diagnosis. Delirium has historically been a general descriptive term akin to metabolic encephalopathy and distinguished from dementia by its fairly abrupt onset, altered sensorium, and association with other medical conditions. However, more recently, delirium has been used specifically to describe a state of fluctuating confusion in hospitalized patients, often in those who are critically ill. The presence of delirium has been associated with worsened clinical outcome in these patients, and some studies have suggested that delirium is itself an independent condition with a pathophysiology and treatment distinct from the many other systemic diseases known to cause metabolic encephalopathy. The neurotransmitter acetylcholine is particularly implicated in delirium.[4] Predisposing factors include older age, dementia, sensory impairment, sleep deprivation, and the use of sedative medications. Inflammatory serum markers and genetic polymorphisms of the apolipoprotein E gene have also been suggested as predictors of presence or duration of delirium. In the intensive care unit, the use of the sedative medication dexmedetomidine has been associated with less delirium than benzodiazepine infusions. Long-term cognitive impairment has been associated with delirium in acutely hospitalized patients, especially those with pre-existing cognitive impairment.[5] It is distinctly uncommon, however, for delirium to lead to a chronic vegetative or minimally conscious state. It remains controversial whether delirium is a target for specific treatment or is principally an indicator of the need for aggressive treatment of underlying medical problems and minimization of sedative usage in the hospital.

Systemic Disorders With Focal Neurologic Manifestations

A variety of systemic disorders may cause alteration of consciousness through either infiltration of the CNS or the presence of discrete lesions. Occasionally, patients may appear clinically to have a diffuse encephalopathy, but close examination reveals focal neurologic signs. In this setting, the distinction between metabolic encephalopathy and diffuse multifocal cerebral disease may be clinically difficult and appear to be only a matter of semantics. Pathologically, however, the processes are quite different, with the latter representing more than just an alteration in substrate delivery or a global process related to circulating systemic factors. The three categories of systemic disease that most often manifest in this manner are collagen vascular diseases, systemic malignancies, and diffuse infections.

Neuropsychiatric complications are frequent clinical manifestations of SLE.[6] Neuropathologic findings in these patients vary from normal to the presence of diffuse microinfarcts. Lupus cerebritis commonly manifests as a focal process with pathologic findings of a bland, and occasionally necrotizing, vasculopathy with perivascular inflammatory infiltrates. There is debate whether this represents a “true” vasculitis or a more infiltrative process surrounding, rather than invading, the vessels. Particular neurologic manifestations depend on lesion location, and aphasia due to focal lesions in the language regions or abulia due to bifrontal lesions are common. Neurosarcoidosis most often manifests as meningeal inflammation or focal cranial neuropathies but can occur as a large cerebral or brainstem mass lesion that affects consciousness.

Systemic cancer affects consciousness in a variety of ways. Cancer may cause metabolic problems related to electrolyte disturbances and primary organ dysfunction. Focal neurologic manifestations in patients with cancer more likely suggest metastatic disease to the CNS, as discussed in Chapter 26. Metastatic brain tumors are much more common than primary brain tumors. Most commonly occurring supratentorially, mass effect from metastases may cause cerebral herniation with brainstem compression or bihemispheric dysfunction. Meningeal carcinomatosis often spares consciousness, except when so extensive that intracranial vessels at the base of the brain are affected, leading to stroke. Cancer treatments themselves may have effects on consciousness. Metabolic encephalopathy may be caused by certain chemotherapeutic agents, and cranial irradiation may result in focal necrosis that may be initially difficult to differentiate from recurrent tumor.

Infection may also cause focal or global neurologic disturbances of consciousness. Brain abscess, meningitis, or encephalitis may occur in otherwise normal individuals or in those with compromised immune systems due to a variety of systemic diseases. Several systemic infections are particularly associated with focal processes or infiltration of the nervous system including human immunodeficiency virus (HIV) infection, syphilis, and Lyme disease. Direct infection of neurons by HIV may result in HIV encephalopathy. Although described as a diffuse encephalopathy, it is probably a “microscopic structural” process related to global infection and infiltration. Progressive multifocal leukoencephalopathy (PML) occurs from infection with the JC papovavirus and manifests principally as cerebral white matter lesions that may involve altered consciousness. Patients immunocompromised from HIV infection are also at risk of a myriad of CNS problems, including primary CNS lymphoma, toxoplasmosis, and other opportunistic infections, discussed further in Chapter 44. Syphilis may have a variety of CNS manifestations; consciousness may be affected by strokes in meningovascular syphilis, and dementia occurs in tertiary syphilis. Lyme neuroborreliosis may cause generalized confusion that has been mistaken for psychiatric disease. Like a number of other systemic disorders including SLE, sarcoidosis, PML, and syphilis, Lyme disease may have the neuroimaging appearance of diffuse cerebral white matter (or demyelinating) lesions, and therefore, may mimic multiple sclerosis.

Systemic Diseases Presenting as Primary Neurologic Disorders

Seizures, stroke, and acute mass lesions are primary neurologic disorders that may occur secondary to systemic diseases. Generalized seizures, by definition, result in alteration or loss of consciousness. Stroke and acute mass lesions may cause alterations in consciousness depending on their location. Although systemic diseases such as hypertension and diabetes are implicated in the genesis of stroke, cancer is implicated in metastatic CNS disease, and many systemic disorders cause seizures, certain conditions have primary neurologic diagnoses as their principal manifestation. An example of a systemic disorder that may present initially with seizures or severe encephalopathy is hemophagocytic lymphohistiocytosis (HLH). A form of severe excessive immune activation, HLH often has systemic manifestations such as hepatic or renal impairment and may be associated with hematologic or solid malignancies or rheumatologic disorders. Magnetic resonance imaging (MRI) of the brain often shows scattered lesions on T2-weighted imaging, and CSF is abnormal in about half of cases.

Large-vessel ischemic strokes may occur from either embolic or thrombotic causes. Infective endocarditis or marantic endocarditis (as in SLE or cancer) may result in embolic infarction that may alter consciousness depending on stroke location and size, as discussed in Chapter 6. Hypercoagulable states may occur in cancer or autoimmune disorders and cause thrombotic large-vessel occlusion of the cerebral arterial circulation. Hypercoagulability may also lead to thrombosis of the cerebral venous sinuses; alterations in factors V and VIII as well as proteins C and S during a protein-losing enteropathy such as during an ulcerative colitis flare are a potential cause. Leukemia with white blood cell counts in excess of 100,000/μL, polycythemia vera with hematocrit greater than 55 percent, and essential thrombocythemia with a platelet count above 1,000,000/μL may each increase blood viscosity leading to thrombotic occlusion. Small-vessel or lacunar infarcts rarely result in alterations in consciousness. Cerebral vasculitis, however, is often associated with confusion and alteration in behavior and the content of consciousness due either to large-vessel stroke or, more commonly, to widespread mid-size and small-vessel infarction. Although cerebral vasculitis may occur in isolation (e.g., granulomatous angiitis of the nervous system), numerous connective tissue disorders, including polyarteritis nodosa and Churg–Strauss syndrome, may be implicated (see Chapter 50).

Cerebral mass lesions that lead to a decrease in the level of consciousness usually develop rapidly. Primary and secondary brain tumors may manifest in this manner, but acute intracranial hemorrhage is the most common responsible lesion. Hypertension is the most common cause of intracerebral hemorrhage. Coagulopathy in the setting of liver failure, disseminated intravascular coagulation, or thrombotic thrombocytopenic purpura may precipitate a spontaneous intracerebral, subdural, or epidural hematoma. Mild head trauma, which would otherwise be well tolerated, may lead to severe intracranial bleeding with subdural or intraparenchymal hematoma formation if a concomitant coagulopathy is present.

APPROACH TO PATIENTS WITH DISORDERED CONSCIOUSNESS

The fundamental goal of evaluation of patients with disorders of consciousness is to distinguish processes that may cause ongoing brain injury from those that are reversible if concurrent systemic diseases are treated adequately. The manifestations of systemic diseases in the CNS are protean, and "benign" and "malignant" causes of altered consciousness may appear clinically similar. Thus, an orderly approach to the evaluation of patients is essential for timely and accurate diagnosis, which can direct focused treatment. The approach should combine clinical neurologic assessment with judicious use of other diagnostic studies including neuroimaging, electrophysiologic evaluation, CSF analysis, and other laboratory tests.

Neurologic History and Examination

The neurologic findings in patients with altered consciousness and the time course of onset are the principal components of patient assessment. All supporting studies, regardless of their nature, must be interpreted within the context of the neurologic examination. The neuroanatomy of consciousness forms the underpinning for neurologic assessment, and it is this localization that allows the formation of a differential diagnosis. The first step is to define whether the primary disturbance is of content or arousal.

When content of consciousness is impaired in patients who are alert and without marked decrease in the level of consciousness, neurologic assessment focuses on higher cortical function. Abnormalities of language, visuospatial orientation, and visual fields suggest a focal cerebral cortical lesion. Disordered attention, concentration, and short-term memory usually indicate a more global process involving both cerebral hemispheres. In the former case, stroke, tumor, a demyelinating process, or focal abscess should be considered, and neuroimaging may be diagnostic. In disorders of global cerebral content, a diffuse process is implicated; depending on the history and associated medical and neurologic findings, a primary neurologic process such as Alzheimer disease or a global metabolic encephalopathy from organ dysfunction, medications, or postictal state may be responsible.

The more urgent circumstance occurs in patients with decreased level of arousal, especially coma. Processes, either structural or metabolic, that develop acutely tend to involve a disproportionately decreased level of consciousness compared with those that develop over much longer periods of time. The initial focus of the neurologic examination of the stuporous or comatose patient should be in defining the anatomic localization of the process, distinguishing between brainstem (RAS) and bihemispheric disease. This is also often the distinction between structural (usually RAS) and metabolic (usually bihemispheric) causes of coma. A notable exception is the locked-in state, in which a structural lesion, usually a stroke, involves the brainstem but spares the RAS.[7] Patients who are "locked in" are not comatose and may have intact consciousness; motor function in the form of eye opening and blinking is usually retained, whereas horizontal ocular movements and appendicular motor function are typically absent. Thus, the first step in clinical evaluation of the apparently comatose patient is to exclude the possibility of the locked-in syndrome, which is suggested by the observation that the patient can open their eyes and blink to command.

Once coma is established, assessment of brainstem and motor function can proceed. Abnormalities of pupillary function, ocular motility, corneal and gag reflexes, and respiratory function help distinguish an intact from an impaired brainstem. Preserved pupillary function is a hallmark for distinguishing between metabolic and structural causes of coma. Reflexive ocular movements (oculocephalic reflexes tested with "doll's eyes" or "cold caloric" maneuvers) are typically preserved in metabolic coma. Occasionally, however, odd conjugate downgaze, skew deviation, and loss of ocular reflexes are found in deep coma caused by metabolic disorders, especially liver failure or sedative drug overdose. Unilateral absence of the corneal or gag reflex suggests structural brainstem impairment. Motor function is symmetric in coma of metabolic origin. Depth of coma, regardless of cause, may determine whether purposeful response to pain is present. Gross asymmetry of purposeful or reflex motor response to pain suggests a structural process. Patients in deep coma of metabolic cause, especially from sedative drug overdose, may exhibit symmetric flexor or extensor posturing, with retained brisk pupillary reflexes and intact brainstem reflexes.

Neuroimaging

Findings on clinical examination direct the need for, and type of, neuroimaging. Most patients without a history of head trauma who are somnolent with a global alteration in cognitive function and intact brainstem reflexes have a metabolic encephalopathy. When a known systemic cause of metabolic encephalopathy, such as uremia, liver failure, or sedative or other drug use, is present, neuroimaging may not be necessary. Conversely, all patients with coma of unknown etiology require urgent head imaging.

The principal value of early neuroimaging is to evaluate for structural processes. Computerized tomography (CT) is particularly effective at demonstrating acute intracranial hemorrhage and in most centers is more easily obtained in neurologically impaired patients than MRI; therefore noncontrast CT is the best first option for neuroimaging in patients with acute alteration or loss of consciousness. CT in acute stroke (within the first 12 hours) may be normal or show only subtle abnormalities such as loss of gray–white differentiation or mild edema. CT is greater than 93 percent sensitive for subarachnoid hemorrhage within the first day following aneurysm rupture, and nearly always shows acute intraparenchymal or extra-axial processes such as hemorrhage and mass lesions that are causing cerebral herniation. By contrast, head CT in metabolic encephalopathy is usually negative or nondiagnostic.

MRI is much better than CT at delineating specific anatomic structures, especially in the posterior fossa. It is usually not necessary in the emergency setting when CT has been performed. An important exception is when cerebral venous sinus thrombosis is suspected; CT with contrast demonstrates a sign known as the "empty delta" in approximately 30 percent of cases; this represents clot in the torcula, where the superior sagittal sinus meets the paired transverse sinuses.[8] However, MRI with contrast, especially when done with magnetic resonance venography, is highly sensitive and specific for thrombosis of the sagittal sinus or other intracranial venous sinus that might be the cause of coma. Contrast CT venography is also an option. For patients in whom altered consciousness or coma is not acute, MRI may be preferable to CT because it is more likely to reveal cerebral metastases, subtle signs of infection or cerebral swelling, or changes that are sometimes seen in certain metabolic conditions, such as basal ganglia abnormalities in liver disease or posterior white matter changes in hypertensive encephalopathy or eclampsia.

Electrophysiologic Studies

EEG and evoked potentials are the major electrophysiologic modalities of diagnostic use in patients with altered consciousness. They are used mainly to exclude seizures (especially nonconvulsive status epilepticus), to confirm the diagnosis of certain metabolic encephalopathies that may have characteristic EEG patterns, and to provide a guide to prognosis in irreversible cerebral injuries, especially hypoxic-ischemic encephalopathy. EEG is indicated in patients with coma of unknown etiology, especially those who have nondiagnostic head imaging studies.

Nonconvulsive status epilepticus is a disorder in which generalized seizures continue without gross motor manifestations of convulsions. This may occur in patients who present with clinically apparent seizures and then continue to seize even after clinical evidence of convulsions ceases. It includes patients with frequent complex partial seizures or absence status (spike-wave stupor). Subclinical electrographic seizures may be identified in up to 20 percent of patients with significant primary neurologic injuries (such as stroke or traumatic brain injury) who undergo continuous EEG monitoring in the neurologic intensive care unit. Studies of inpatients with primarily medical illness outside the intensive care unit have found electrographic seizures in 7 to 10 percent of those monitored with EEG.[9] Although this form of status epilepticus as the sole reason for decreased level of consciousness is uncommon, the diagnosis cannot be made without an EEG. Overt status epilepticus, especially myoclonus or nonconvulsive status, after a hypoxic-ischemic cerebral insult usually carries a poor prognosis.

Metabolic encephalopathies have a relatively uniform pattern on EEG, with diffuse bilateral slowing of the background rhythm. As metabolic coma deepens, amplitude may decrease. Triphasic waves may be found in hepatic encephalopathy but are nonspecific and present in other metabolic encephalopathies, including uremic and septic encephalopathies. In patients with hepatic encephalopathy who are receiving flumazenil as a diagnostic or therapeutic maneuver, EEG monitoring can demonstrate return of more normal background rhythms concurrent with improvement in level of consciousness. As with nonconvulsive seizures, other features such as lateralized or generalized periodic discharges may occasionally be seen on EEG in patients with severe metabolic encephalopathies.

Evoked potential monitoring is usually reserved for the evaluation of comatose patients. Short-latency somatosensory evoked potentials (SEPs) are typically preserved in reversible metabolic encephalopathies. However, in conditions that cause neuronal death, they may be abnormal and of prognostic value. In hypoxic-ischemic encephalopathy, bilateral absence of the N20 component of the somatosensory evoked potential (SSEP) to median nerve stimulation is strongly predictive of a very poor neurologic outcome (see Chapter 9). However, timely availability and variable expertise in interpretation remain shortcomings to widespread implementation.

Cerebrospinal Fluid and Other Laboratory Studies

Prior to the development of CT and MRI, lumbar puncture was a standard part of the investigation of patients with alterations in consciousness. Lumbar puncture is currently performed selectively when meningitis and encephalitis are diagnostic possibilities or when the etiology of coma remains elusive despite clinical evaluation, laboratory testing, and neuroimaging. In comatose patients, neuroimaging should be performed before lumbar puncture because of the rare but potential risk of precipitating transtentorial herniation.

Lumbar puncture may be of particular diagnostic utility in patients with an altered level of consciousness related to unsuspected cerebral venous sinus thrombosis from a hypercoagulable state, in which an elevated opening pressure may be the first diagnostic clue of increased intracranial pressure due to venous outflow obstruction. Analysis of the CSF may also be helpful for evaluation for suspected neurosyphilis, Lyme disease, and neurosarcoidosis. In other conditions such as HIV encephalopathy, CSF cell counts may be mildly elevated. A CSF pleocytosis may rarely be present after seizures, even when no apparent CNS infection is present, but this is uncommon and remains a diagnosis of exclusion.

Laboratory testing of serum glucose, electrolytes and of renal and liver function is a fundamental part of the evaluation of all patients with alterations in consciousness. It is important that metabolic derangements found on laboratory testing match the neuroanatomic localization of the patient's syndrome; otherwise, further laboratory, neuroimaging, electrophysiologic, and CSF testing may be required. For example, a patient with liver failure, unilateral impairment of ocular reflexes, and a hemiparesis requires urgent neuroimaging to rule out an intracranial mass lesion such as an acute hematoma, especially because patients with liver failure often have concurrent coagulopathy. Also, when the degree of electrolyte abnormality does not correlate with the depth of alteration in consciousness (e.g., deep coma with a mildly depressed serum sodium concentration), more extensive neurodiagnostic testing should occur.

Diagnosis and Treatment: Coordinated Clinical Approach

The major concern in the management of patients with altered consciousness is preservation or restoration of brain function. The resuscitation principles of maintaining the airway, breathing, and circulation should always be attended to first. By ensuring oxygenation, ventilation, and adequate brain and tissue perfusion, impaired substrate delivery to the brain may be restored and secondary brain injury limited.

A fingerstick or serum glucose level should be performed urgently in all patients with new-onset coma or stupor in order to rule out hypoglycemia as a cause or contributing factor. Neurologic examination should then proceed. Urgent hematologic and biochemical screening tests, including renal and possibly hepatic function studies, should be performed concurrently with neuroimaging, usually CT scanning. Based on these results, EEG and lumbar puncture can be considered. If alteration in consciousness is mild or of relatively long standing, investigation can proceed less urgently.

PROGNOSIS

Prognostication of outcome gives physicians, patients, and families reasonable expectations that can aid in decisions to proceed with, or limit, medical care. It is essential that the prognosticator keep in mind the continuum of prognosis and outcome, recognizing that what would be considered a poor prognosis to some may be acceptable to others.

Coma is one of the most compelling neurologic conditions in which prognostication is often sought. The most important overall determinant of prognosis in coma is the cause of the coma, especially whether the coma is caused by injury to the brain (e.g., from trauma, hypoxia-ischemia, prolonged hypoglycemia) or is secondary to systemic factors (e.g., sedative drug overdose, liver failure, sepsis). In the latter case, prognosis is linked more to the severity of the underlying disease than to the coma itself, although coma in organ failure or sepsis is usually a marker of grave illness that often carries with it a poor prognosis.

There are, however, some general principles to prognostication in coma that may apply across illnesses. There is more information regarding prognosis for hypoxic-ischemic encephalopathy after cardiac arrest than for any other cause of altered consciousness in systemic diseases (see Chapter 9). Historically, specific aspects of the clinical examination performed at different times after resuscitation from cardiac arrest have been used as either the singular or most relied-upon predictors of long-term functional outcome. However, most of these studies were performed prior to the routine use of therapeutic hypothermia and targeted temperature management for severely brain-injured cardiac arrest survivors. While neurologic examination findings of brainstem impairment or motor response no better than extensor posturing to painful stimulus seen 3 to 7 days after resuscitation are still concerning for a poor prognosis, reliance exclusively on the neurologic examination for prognostication after cardiac arrest has been replaced with multimodality prognostication using a range of tests. In addition to the neurologic examination, these may include EEG testing for assessment of background rhythm and reactivity, serum neuron-specific enolase, somatosensory evoked potentials, CT or MRI imaging days after resuscitation, and quantitative pupillometry. No single test is sufficiently reliable for prognostication of a poor outcome to serve as a basis to make decisions to limit care within the first days after resuscitation, and concordance across multiple or all tests is of most utility.[10]

Predictors, either clinical or laboratory-based, for outcome from other causes of metabolic coma are much less available. In a series from several decades ago in which recovery from various forms of coma was assessed, 35 percent of patients with hepatic coma and 34 percent of patients with coma caused by renal failure regained independent function, whereas only 12 percent of patients comatose from hypoxia did so. In another study, it was found that only 8 percent of patients with coma of diverse causes recovered fully or with minimal disability when oculovestibular reflexes were absent. The mortality rate in patients with coma from sepsis-associated encephalopathy and multisystem organ failure approaches 40 percent; this is, however, similar to the mortality rate of multisystem organ failure itself, suggesting that the underlying critical illness, not the presence of coma, defines prognosis in this circumstance. The presence of intact brainstem reflexes (pupils and ocular movements) suggests a more favorable outcome than otherwise in metabolic coma; presumably, these metabolic causes of coma do not usually cause permanent cerebral damage sufficient to cause neuronal death. Most patients who recover from their underlying systemic illness recover completely from coma of metabolic origin. This is not always the case, however, and suggests that some patients with severe critical illness from acute respiratory distress syndrome, sepsis, or electrolyte disturbances may acquire secondary brain injury from either impaired substrate delivery or mechanisms yet to be elucidated.[11]

BRAIN DEATH

The diagnosis of brain death has medical, legal, and ethical implications. In the United States and most other countries, brain death is a prerequisite to most organ donation, although donation following cardiac death is now being used in certain circumstances. Brain death is equivalent to circulatory death (defined by absence of cardiac and respiratory functions) as a medical and legal definition of death, and the time of determination of brain death is considered the time of death. The Uniform Determination of Death Act states that "an individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with accepted medical standards." Despite ample medical and legal precedent for the concept and importance of brain death, several surveys have indicated lack of knowledge and consistent application of clinical definitions and diagnostic criteria. The Quality Standards Subcommittee of the American Academy of Neurology has developed standardized criteria for the determination of brain death in adults, and these form a reasonable, currently accepted medical standard.[12]

The determination of brain death is based primarily on clinical criteria (Tables 61-4 and 61-5), with use of supportive diagnostic tests when necessary. Several prerequisites must be met. It is essential that there be a diagnosis of a CNS catastrophe that is compatible with brain death. These include neurologic disorders (e.g., subarachnoid hemorrhage) and systemic diseases (e.g., hypoxic-ischemic encephalopathy, massive brain edema from fulminant hepatic failure). Complicating conditions that may confound the neurologic examination must be excluded, such as hypothermia (≤36°C), hypotension (systolic blood pressure ≤100 mmHg), drug effects such as from neuromuscular blocking agents or sedatives, and facial or cervical trauma that makes it impossible to perform the neurologic examination.

The three clinical features of brain death, all of which must be demonstrated, are cerebral unresponsiveness, absence of brainstem reflexes, and apnea. Cerebral unresponsiveness is demonstrated by absence of cerebral motor response to painful stimulus (supraorbital and nail-bed pressure in all extremities). Brainstem reflexes that must be demonstrated as absent include pupillary light reflex (usually ≥ 4 mm in size), ocular movement (absent oculocephalic response or "doll's eyes" and absent response to cold caloric testing), facial sensation and motor response (absent corneal reflex), and pharyngeal response (absent gag and cough reflexes). Apnea is confirmed when the $Paco_2$ is documented to rise, following ventilator discontinuation, above 60 mmHg (or 20 mmHg above baseline in patients with chronic carbon dioxide retention) without clinical evidence of respiratory effort, indicating absence of function of central respiratory chemoreceptors and neurons located in the medulla. Independent confirmation by a second physician is required for the clinical diagnosis of brain death.

Several confirmatory laboratory tests may be used in the determination of brain death but do not supersede the clinical examination. The use of confirmatory tests is not required and is usually reserved for patients in whom clinical examination cannot be reliably performed because all conditions that may confound the clinical neurologic assessment cannot be excluded. In patients who have received significant doses of sedative agents (e.g., high-dose barbiturates for treatment of elevated intracranial pressure), clinical examination is unreliable for the diagnosis of brain death. In this circumstance, a cerebral blood-flow study demonstrating absence of blood flow to the brain is sufficient for the diagnosis of brain death.

TABLE 61-4 ■ Conditions to Be Excluded in Using Clinical Criteria for Brain Death

Hypothermia–i.e., temperature ≤36°C

Hypotension/shock–i.e., systolic blood pressure ≤100 mmHg

Hypoxia–i.e., Pao_2 ≤60 mmHg

Sedative drug effects–e.g., high-dose barbiturates

Neuromuscular blocking agents–check peripheral nerve stimulator (for "train-of-four" twitches)

Severe facial trauma–inability to check pupillary or ocular movement function

Severe cervical trauma–high cervical injury interferes with assessment of apnea

TABLE 61-5 ■ Clinical Criteria for Diagnosis of Brain Death

- Diagnosis compatible with brain death (e.g., head trauma, stroke, hypoxic-ischemic encephalopathy)
- All confounding conditions excluded (see Table 61-4)
- Cerebral unresponsiveness: no response to central painful stimulus (supraorbital pressure, temporomandibular joint) in all extremities
- Absence of brainstem reflexes
  - No pupillary reflexes (usually in brain death ≥4 mm in size)
  - No ocular movement (absent doll's eyes or absent response to cold caloric testing)
  - No facial sensation and motor response (absent corneal reflex)
  - No pharyngeal response (absent gag and cough reflexes)
- Apnea: no clinical evidence of respiratory effort when the $Paco_2$ is documented to rise above 60 mmHg (or 20 mmHg above baseline in patients with chronic CO_2 retention)
- Independent confirmation by a second physician

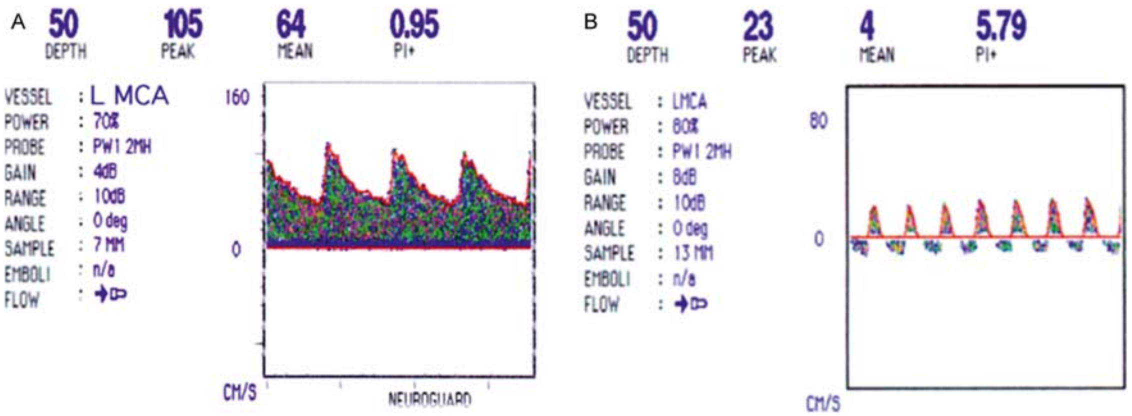

FIGURE 61-2 ■ Diagnosis of brain death by transcranial Doppler ultrasonography (TCD). *A*, Normal blood flow velocity and direction in the left middle cerebral artery (LMCA). *B*, Findings in brain death. Direction of flow is reversed during diastole, indicating cerebral circulatory arrest. For the use of TCD as a confirmatory test in brain death, these findings must be present in both anterior circulations as well as in the posterior circulation.

Formerly, conventional angiography was performed, but currently a nuclear medicine technetium-99m brain scan is often used. Transcranial Doppler ultrasonography (Fig. 61-2) can also be used provided that adequate insonation windows can be obtained. In the absence of sedative medications and hypothermia, EEG performed according to certain specific technical standards can be used when a confirmatory test is necessary.

Some ethical issues remain with regard to brain death. Legally, “irreversible cessation of all functions of the entire brain, including the brainstem” indicates brain death, but it has been left to the medical community to decide how to demonstrate this. When the accuracy of these stated clinical criteria has been reviewed, the diagnosis of brain death has been considered secure. Some have suggested that prolonged unconsciousness or a persistent vegetative state (PVS) is similar to brain death because purposeful consciousness cannot be regained; although these latter circumstances have been supported in terms of withdrawal of medical support and care due to medical futility, they do not meet the medical or legal definitions of brain death and should not be considered equivalent. Some individuals and cultures do not accept the notion of brain death as equivalent to circulatory death, which can present challenges regarding ongoing medical care and the medical—legal interface.

VEGETATIVE AND MINIMALLY CONSCIOUS STATES

Brain death could be considered the ultimate loss of consciousness. The neuroanatomy of brain death requires the loss of function of both cerebral hemispheres and the RAS, although it may not be possible clinically to determine cortical function when the RAS and entire brainstem have been completely destroyed. There are, however, circumstances of permanent loss of consciousness other than brain death. It is uncommon for a sleep-like coma state (eyes closed) to persist for more than 2 to 4 weeks. After this time, patients with permanently disordered consciousness usually evolve to a chronically unresponsive state with eyes open. When subjects exhibit this eyes-open unconsciousness with no awareness of self or the environment for more than 1 to 3 months, the definition of a PVS is met. PVS is also known as the unresponsive wakefulness syndrome (UWS). This state may result from a variety of insults, including acute conditions such as traumatic brain injury, hypoxic-ischemic encephalopathy, and encephalitis, as well as being an end result of chronic neurodegenerative disorders such as Alzheimer disease. Clinically, the UWS appears to involve an intact brainstem and absent cerebral cortical function. Autopsy results have largely confirmed this neuroanatomy, showing extensive cortical and hippocampal damage after hypoxic-ischemic encephalopathy and subcortical diffuse axonal injury after trauma. Occasional reports have demonstrated severe brainstem damage, but not in isolation. However, postmortem examination of a prominent UWS case from the 1980s regarding the right of surrogates to limit ongoing care demonstrated severe bilateral damage to the thalamus, out of proportion to any damage found in the cortex or brainstem, suggesting that the thalamus is important for cognition and that severing the connections between the RAS and cerebral cortex may be sufficient to impair consciousness, perhaps permanently. Thus, different neuroanatomic lesions may lead to the clinical picture of a PVS/UWS and perhaps even the clinical diagnosis of brain death.

It is now clearly recognized that some patients evolve to a clinical state in which they remain severely impaired and unable to perform functionally useful activity and self-care, despite demonstrating evidence of behavioral consciousness and interaction with their environment. This state is known as the *minimally conscious state* and, in contrast to the vegetative state, patients in this state may follow occasional commands, reach for objects, localize noxious stimuli, or demonstrate contingent vocalization, smiling, or crying. Because these activities may be only partially present and able to be performed only intermittently, distinguishing the vegetative and minimally conscious states may be clinically challenging. However, this clinical distinction is important. While patients who meet the definition of chronic vegetative state after a year or more are unlikely to improve, some patients in a prolonged minimally conscious state do show delayed improvement, especially if traumatic brain injury is the initial cause. Unfortunately most of these patients still remain in a state of severe disability.

The concept of distinguishing vegetative from minimally conscious states may additionally be of ethical importance as minimally conscious patients are awake, may perceive pain, and may raise concerns among families and caregivers regarding patient-level communication and long-term care goals. The best way to distinguish these states is through prolonged and multiple neurologic examinations by different examiners who can objectively document their findings. Interestingly, several recent studies have examined functional neuroimaging using functional MRI or positron emission tomography in these two patient groups.[13] In one study including 54 patients, 5 patients (4 diagnosed clinically as vegetative and 1 as minimally conscious, all as a result of trauma) were able to willfully modulate brain activity seen on functional MRI in response to verbal questions, with activity primarily seen in the supplementary motor area or the parahippocampal gyrus, depending on whether the directions were related to motor or sensory imagery.[14] No patient in a vegetative state or minimally conscious state from hypoxic-ischemic brain injury in this study demonstrated willful modulation of brain activity. Another recent study found EEG activation in 15 percent of acutely brain-injured patients who were clinically unresponsive to spoken commands.[15] A single-patient study, in which a patient in a minimally conscious state 6 years after traumatic brain injury underwent thalamic stimulation with an implantable deep brain stimulator, found improvement in arousal and motor control. The use of brain–computer interfaces to help patients in minimally conscious states interact with their environment is an area of evolving research.

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CHAPTER

62

Dementia and Systemic Disease

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CAUSES OF DEMENTIA
- Alzheimer Disease
- Vascular Dementia
- Synucleinopathies
  - *Dementia With Lewy Bodies*
  - *Parkinson Disease*
  - *Multiple System Atrophy*
- Tauopathies
  - *Frontotemporal Dementia*
  - *Progressive Supranuclear Palsy*
  - *Corticobasal Degeneration*
  - *Chronic Traumatic Encephalopathy*
- Systemic Diseases Causing Dementia

SYSTEMIC COMPLICATIONS OF DEMENTIA
- Dysphagia and Aspiration
- Agitation and Delirium
- Depression and Other Mood Disorders
- Falls
- Orthostatic Hypotension
- Sleep Disorders
- Gastrointestinal and Genitourinary Complications

Dementia is a common problem among the elderly and is associated with a number of important systemic complications. Epidemiologic studies estimate the prevalence of Alzheimer disease, the most common form of dementia, in the United States to be approximately 3 percent between ages 65 and 74, 17 percent between ages 75 and 84, and 32 percent over age 84, which ensures that nearly every physician will encounter patients with dementia.[1] Alzheimer disease is the sixth leading cause of death in the United States and continues to increase in prevalence with an aging population.[1] The purpose of this chapter is to review the causes of dementia and the systemic problems that result in order to arm practitioners with the tools necessary to care effectively for this vulnerable patient population.

CAUSES OF DEMENTIA

Most dementias are the result of progressive neurodegenerative diseases (Table 62-1). These conditions usually lead to death within 5 to 10 years of clinical onset.[1] Patients may also acquire dementia after a temporally isolated event such as a severe traumatic brain injury or encephalitis. In such cases, the dementia is not progressive, and some recovery or adaptation can be expected over time. Dementia may also be reversible when caused by certain treatable systemic conditions; these cases are especially important to recognize, diagnose, and treat.

Alzheimer Disease

Alzheimer disease is the most common cause of dementia in the elderly. The disorder almost invariably begins with insidiously progressive short-term memory loss followed by diminished cognitive function in a range of domains that most often include language, visuospatial ability, and praxis. Memory loss is often initially misattributed to normal aging, often leading to a delay in diagnosis. Symptoms are more closely linked to the relative density of tau neurofibrillary tangles than β-amyloid plaques in different brain regions; the highest density of tangles is usually found in the medial temporal lobes, regions critical for the formation of new memories. Other frequently involved areas include the parietal lobes, which are involved in visuospatial processing. The course is relentlessly progressive and universally fatal,

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TABLE 62-1 ■ Common Causes of Dementia

Pathology	Disease
Neurodegenerative Diseases	
β-Amyloid, tau	Alzheimer disease
Tauopathy	Frontotemporal lobar degeneration Progressive supranuclear palsy Corticobasal degeneration Chronic traumatic encephalopathy
Synucleinopathy	Dementia with Lewy bodies Parkinson disease Multiple system atrophy
Chronic ischemia	Vascular dementia
Transactive response DNA-binding protein 43 (TDP-43)	Frontotemporal lobar degeneration
Fused in sarcoma protein	Frontotemporal lobar degeneration
Treatable Causes of Dementia	
Infectious	Chronic meningitis (e.g., mycobacterial, fungal) HIV infection Neurosyphilis (general paresis)
Metabolic	Hypothyroidism Vitamin B_{12} deficiency Obstructive sleep apnea
Psychiatric	Depression
Structural	Hydrocephalus Chronic subdural hematoma Brain tumor

leading to death within 4 to 8 years from the time of diagnosis.[1] Death is often from aspiration pneumonia or other complications of the bed-bound end-stage of the illness. While social graces are usually preserved early in the course of the illness, behavioral problems such as aggression, agitation, and episodic delirium often emerge in later stages and are particularly problematic for caretakers. Falls are also common when patients develop postural instability later in the disease course.

Risk factors for Alzheimer disease include age, the presence of the APOE ε4 allele, having a first-degree relative with the disease, low educational attainment, traumatic brain injury, tobacco use, hearing loss, diabetes, hypertension, obesity, hypercholesterolemia, sleep-disordered breathing, social isolation, and depression.[2] Factors associated with reduced rates of the disease include regular exercise, social engagement, and higher educational attainment.[2] Whether addressing these risk factors prevents Alzheimer disease remains unclear. Less than 1 percent of cases are inherited in an autosomal dominant pattern and these are mainly caused by mutations in the genes encoding amyloid precursor protein, presenilin 1, and presenilin 2.[1] There is no treatment that halts the progression of the disease. Centrally-acting acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, and the *N*-methyl-D-aspartate receptor antagonist memantine will boost cognition at various stages of the illness and may as a result temporarily improve quality of life or delay nursing home placement, although clinical effects are marginal.[2]

Vascular Dementia

Cerebrovascular disease carves several paths to dementia. The accumulation of multiple large-territory infarctions in the setting of atrial fibrillation, intracranial atherosclerosis, or other causes of recurrent large-vessel ischemic stroke results in dementia with cognitive deficits referable to the infarcted brain territories. Because dementia progresses with each successive stroke, patients may demonstrate a stepwise decline in function. These patients rarely present to medical care with unexplained cognitive complaints because they are already known to have suffered multiple infarctions.

More common among patients presenting with memory or cognitive dysfunction is dementia resulting from the accumulation of innumerable ischemic lesions in the subcortical and periventricular white matter due to chronic small-vessel disease. The clinical syndrome is one of slowly progressive frontal lobe dysfunction, with problems in working memory and executive function. Involvement of the basal ganglia may result in a shuffling gait and postural instability that resembles parkinsonism. Pathologic examination reveals chronic ischemia with arteriolosclerosis and often amyloid angiopathy of small arterioles. Vascular dementia in many series is the second most common cause of dementia in North America and Europe, accounting for nearly 15 percent of cases.[3]

The incidence of vascular dementia increases with age, and patients are more likely to have hypertension, diabetes, hyperlipidemia, atrial fibrillation, obesity, or a history of tobacco use.[3] Vascular dementia is associated with chronic kidney disease, coronary artery disease, and peripheral vascular disease, although these associations may be mediated by common risk factors. No treatment is known to slow its progression, but physical activity may be protective against its development.[3] It is not known whether aspirin, smoking cessation, or treatment of vascular risk factors prevents or slows the progression of dementia, but these are all standard aspects of secondary stroke prevention and are therefore often a part of the treatment plan for patients with vascular dementia. Donepezil, rivastigmine, galantamine, and memantine have a modest benefit in vascular dementia similar to their effect on cognitive function in Alzheimer disease, but no benefit on global functioning.[3]

Synucleinopathies

The synucleinopathies include dementia with Lewy bodies, Parkinson disease, and multiple system atrophy. The pathologic hallmark of all synucleinopathies is the Lewy body, composed primarily of insoluble α-synuclein aggregates. These aggregates are not common in normal aging; α-synuclein itself is a normally soluble neuronal protein with uncertain function. The role of Lewy bodies and α-synuclein in the pathogenesis of disease is also not well understood.

Parkinsonism is a prominent early feature of most synucleinopathies and describes a clinical syndrome consisting of rigidity, bradykinesia, postural instability, and resting tremor. Rapid eye movement (REM) sleep behavior disorder, in which brainstem projections to the spinal cord that induce atonia during REM sleep are disrupted, causing patients to act out their dreams in dramatic fashion, is another symptom common to the synucleinopathies. REM sleep behavior disorder can precede the onset of parkinsonism in the synucleinopathies by many years.[4] Dysautonomia (e.g., postural hypotension, constipation, urinary incontinence), olfactory dysfunction, and mood disorders are also common early features of this group of disorders.

DEMENTIA WITH LEWY BODIES

Dementia with parkinsonism is the hallmark of this disorder. This diagnosis is likely when cognitive dysfunction manifests prior to or within 12 months following the onset of parkinsonism. Other core features include well-formed visual hallucinations (often of animals), fluctuations in alertness and cognition, and REM sleep behavior disorder.[4] Periodic unresponsiveness is often mistaken for syncope or seizure. Cognitive dysfunction consists of impaired visuospatial ability, attention, and executive function, with relatively preserved memory early in the disease course. Patients are exquisitely sensitive to dopamine antagonists and can develop prolonged encephalopathy and rigidity after exposure to relatively small doses of neuroleptics. Donepezil and rivastigmine are effective at ameliorating the cognitive symptoms and are often titrated to higher doses than those used for Alzheimer disease. The rate of progression is similar to Alzheimer disease although survival after diagnosis may be slightly shorter in Lewy body dementia.

PARKINSON DISEASE

Parkinson disease is a slowly progressive motor disorder in which dementia is usually a late feature. There is degeneration of dopaminergic neurons in the substantia nigra pars compacta in the midbrain. The prevalence of dementia in patients with this disease is approximately 30 percent, and it usually manifests a decade or more into the illness. Clinical features may echo those of Lewy body dementia, although memory dysfunction is sometimes more prominent. Cholinesterase inhibitors modestly improve cognitive symptoms in Parkinson disease dementia.[4]

MULTIPLE SYSTEM ATROPHY

Multiple system atrophy is categorized into two subtypes based on the predominant motor features: parkinsonian (MSA-P, previously known as striatonigral degeneration) and cerebellar (MSA-C, previously olivopontocerebellar atrophy). Both are characterized by a progressive decline in multiple neurologic systems and include autonomic dysfunction manifested by urinary incontinence, erectile dysfunction, orthostatic hypotension, and central sleep apnea; bulbar dysfunction manifested by dysphagia; and either prominent cerebellar ataxia or parkinsonism. Dementia occurs in up to 20 percent of patients with multiple system atrophy and tends to feature executive and visuospatial dysfunction.[5] The course is typically more rapid than that of Parkinson disease and similar to Lewy body dementia and Alzheimer disease.

Tauopathies

The tauopathies are a group of neurodegenerative diseases associated with an abnormal aggregation of tau protein in the brain. The most common is Alzheimer disease, considered separately above.

FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia is a clinically, pathologically, and genetically diverse disorder. On neuropathologic

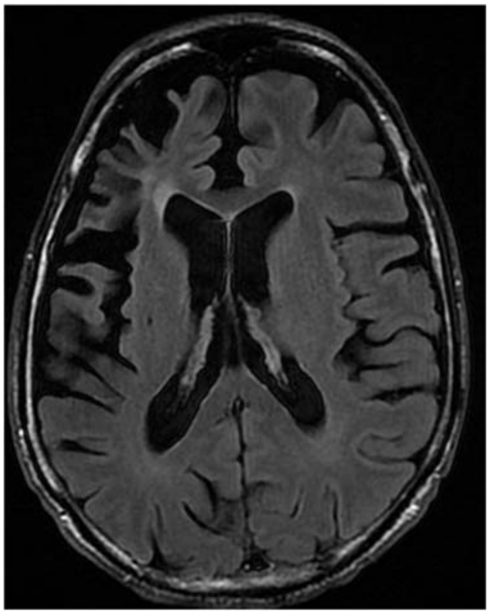

FIGURE 62-1 ■ Frontotemporal dementia. T1-weighted magnetic resonance image of the brain demonstrates atrophy of the nondominant (*right*) frontal lobe out of proportion to other areas.

examination, many cases are associated with inclusions containing tau, a microtubule stabilizing protein.[6] The neuropathology in other cases with similar clinical phenotypes demonstrates inclusions containing TAR DNA-binding protein of 43 kDa (TDP-43) and no tau staining; others are tau negative and TDP-43 negative but positive for the protein fused in sarcoma; and still others are tau negative, TDP-43 negative, fused in sarcoma negative, and ubiquitin positive.[6] Because of overlap between clinical and pathologic subtypes, it is difficult to predict an individual patient's pathology with certainty using current diagnostic techniques, but in general the clinical syndromes associated with tau inclusions are behavioral variant frontotemporal dementia, progressive nonfluent aphasia, progressive supranuclear palsy (PSP), and corticobasal syndrome. Semantic dementia, a variant of frontotemporal dementia with progressive impairment in naming and single-word comprehension, is usually associated with TDP-43 pathology. Many TDP-43-positive cases have comorbid motor neuron disease. There are no specific treatments.

The average age of onset is between 50 and 60 years; the incidence does not increase with age. Frontotemporal dementia accounts for a significant proportion of dementia cases in people aged 45 to 65. The time between onset of symptoms and death is slightly shorter than that in Alzheimer disease. The behavioral variant presents with personality changes, apathy or impulsivity, emotional blunting, loss of empathy and social awareness, lack of insight, mental rigidity, change in eating habits, and poor personal hygiene, all reflecting degeneration predominantly of the nondominant frontal and temporal lobes (Fig. 62-1). When the pathologic process affects the dominant hemisphere, progressive nonfluent aphasia is the typical phenotype and is associated with fewer behavioral changes and more prominent language difficulties.

PROGRESSIVE SUPRANUCLEAR PALSY

Falls are often the earliest symptom in patients with this disorder because of axial rigidity and vertical gaze palsy, the combination of which results in significant postural instability. Other motor symptoms include gait freezing, bradykinesia, rest tremor, apraxia of eyelid opening, dysphagia, and apraxia of speech.[5] Cognitive dysfunction is characterized by a frontal lobe syndrome with executive dysfunction and deficits in working memory, judgment, multitasking, and cognitive processing speed.[5] Neuropsychiatric symptoms also include apathy, disinhibition, dysphoria, and anxiety. Patients are often first misdiagnosed with Parkinson disease, but the diagnosis becomes clear due to the lack of rest tremor, development of a vertical gaze palsy, relatively rapid progression (the median time from onset to death is approximately 8 years), and poor response to dopamine.

CORTICOBASAL DEGENERATION

The term corticobasal degeneration is reserved for patients with a specific pathologic diagnosis, the hallmark of which is tau inclusions. In life, corticobasal degeneration is clinically heterogeneous; patients may present with behavioral variant frontotemporal dementia, progressive nonfluent aphasia, or a more classic corticobasal syndrome that includes asymmetric dystonia and rigidity, isolated limb myoclonus, apraxia, neglect, alien limb phenomenon, and dementia with features similar to PSP.[5] Conversely, some patients diagnosed in life with corticobasal syndrome are found to have Alzheimer disease, PSP, or TDP-43 pathology at autopsy.

CHRONIC TRAUMATIC ENCEPHALOPATHY

A specific pattern of perivascular intracellular phosphorylated tau aggregates can be found at autopsy in the cerebral cortex of patients exposed to repeated head trauma. This pathologic finding is termed chronic traumatic encephalopathy (CTE), and a dose-dependent relationship appears to exist between amount of exposure to head trauma and severity of the neuropathologic findings.[7] The clinical significance of CTE is an area of ongoing research, and validated clinical diagnostic criteria do not yet exist. Patients with CTE at autopsy often demonstrated mood disorders and problems with memory and executive function during life. The age of onset tends to be earlier than that of Alzheimer disease and the course can be progressive or static.

Systemic Diseases Causing Dementia

A number of systemic disorders may cause cognitive decline and mimic Alzheimer disease or other neurodegenerative diseases. These disorders are of importance because they are often treatable. Cognitive decline in most of these conditions is chronic, although occasionally patients present subacutely. Subacute severe cognitive decline, also referred to as rapidly progressive dementia, has a much wider differential diagnosis that is beyond the scope of this chapter.

Cognitive dysfunction is an increasingly recognized neurologic complication of *human immunodeficiency virus (HIV) infection*, discussed in Chapter 43. Previously known by such terms as AIDS dementia complex and HIV encephalopathy, the currently accepted terminology is HIV-associated neurocognitive disorder, with three stages of disease defined based on neuropsychologic testing: asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia. Cognitive impairment is described as subcortical, with impaired information-processing speed, multitasking, decision-making, working memory, and verbal fluency. While the incidence of HIV-associated dementia has declined in the era of antiretroviral therapy, the milder subtypes continue to be common, with 33 percent of patients having asymptomatic neurocognitive impairment and 12 percent mild neurocognitive disorder in a large cohort, raising concern that HIV-associated neurocognitive disorder may represent the effect of a reservoir of viral replication sequestered behind the blood–brain barrier. Patients with progressive neurocognitive decline despite suppression of plasma HIV viral load may have detectable HIV RNA in the CSF; in such patients modifying the antiretroviral regimen based on the genotype resistance profile of HIV in the CSF and the regimen's CNS penetration effectiveness may lead to stabilization of the neurocognitive syndrome. According to guidelines from the United States Preventive Services Task Force, HIV screening should be a routine part of healthcare maintenance and, by extension, testing is reasonable in any patient presenting with cognitive symptoms.

Public health efforts directed at screening and treatment have led to a decline in the prevalence of the neurologic complications of *syphilis* (Chapter 39). Tertiary syphilis is therefore a less important cause of dementia than in the past. General paresis, or the dementia caused by syphilis, is a result of direct infection of neural tissue by *Treponema pallidum* and occurs decades after the primary infection. Patients develop progressive memory loss and personality change. Because nontreponemal tests such as the rapid plasma reagin and Venereal Disease Research Laboratory can be negative in late syphilis, a treponemal test such as the fluorescent treponemal antigen absorption and a lumbar puncture should be performed when the disease is suspected. Lymphocyte count and protein concentration are usually elevated in the spinal fluid.

Rarely, *chronic meningitis* such as that caused by *Mycobacterium tuberculosis* (Chapter 40) or *Cryptococcus neoformans* (Chapter 45) may lead to chronic cognitive decline. Usually the dementia in these cases is accompanied by systemic symptoms of chronic infection such as weight loss, night sweats, and occasional fever. Cognitive symptoms typically have features of delirium including waxing and waning levels of alertness and attention. These conditions are readily distinguished from neurodegenerative diseases with a lumbar puncture demonstrating inflammatory spinal fluid.

In addition to fatigue, cold intolerance, hair loss, myxedema, and weakness, *hypothyroidism* is associated with cognitive dysfunction. The symptoms are usually slowed cognitive processing, impaired learning, and depression. The disorder is readily diagnosed by checking serum levels of thyroid-stimulating hormone.

Deficiency of vitamin B_{12} is associated with an increased risk of developing Alzheimer disease, vascular dementia, and Parkinson disease, but there is no compelling evidence that treatment of the deficiency prevents the development of dementia or improves outcomes in patients who have already developed it. However, there are rare cases of patients presenting with dementia and vitamin B_{12} deficiency who have demonstrated sustained recovery following vitamin supplementation, and therefore a trial of this benign treatment is a reasonable approach to these patients.

Structural lesions such as a chronic subdural hematoma, tumors, and hydrocephalus may also lead to dementia. It is for this reason that brain imaging is part of the standard work-up for dementia. Although subdural hematoma may present with seizures or focal neurologic deficits, in some cases the hematoma expands slowly and causes only cognitive symptoms, with subtle or no motor signs. Similarly, brain tumors can mimic neurodegenerative disease, with slow-growing low-grade tumors more likely to do so than glioblastoma or metastases. Symptoms depend on the location of the tumor. Frontal tumors may cause behavioral symptoms such as apathy, loss of insight and judgment, and difficulty with working memory and executive function. Temporal lesions may result in progressive aphasia and memory loss.

Communicating hydrocephalus is associated classically with the triad of dementia, incontinence, and gait disorder, but patients often present with only one of these symptoms. The dementia is typically characterized by frontal lobe dysfunction with symptoms similar to those seen in vascular dementia, although descriptions of large series with robust cognitive testing are lacking. The gait disorder is typically that of gait initiation failure, often described as a magnetic gait, where the feet appear stuck to the floor. Treatment is placement of a ventriculoperitoneal shunt. When the diagnosis is suspected after careful correlation between the history, neurologic findings, and brain imaging demonstrating ventriculomegaly out of proportion to sulcal atrophy (Fig. 62-2), a lumbar puncture should be performed. Because hydrocephalus with elevated intracranial pressure can lead to an identical clinical presentation, measurement of the opening pressure is critical. A good response to ventriculoperitoneal shunt is predicted if the patient's symptoms improve after a large volume (30 to 50 ml) of cerebrospinal fluid is removed. Importantly, many cases of so-called normal-pressure hydrocephalus will turn out to be early presentations of a neurodegenerative condition; this possibility should be excluded rigorously.

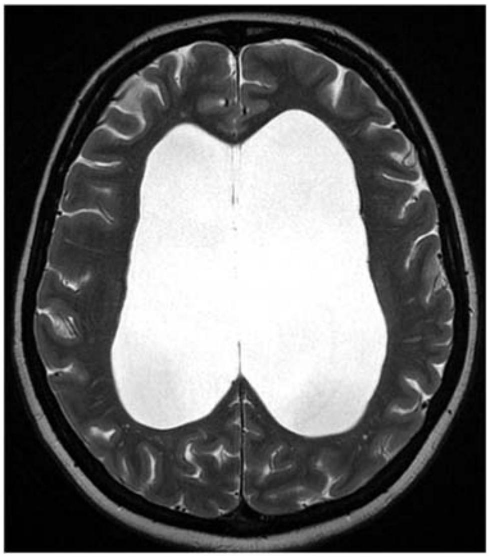

FIGURE 62-2 ▪ Communicating hydrocephalus. T2-weighted MRI of the brain showing ventriculomegaly out of proportion to sulcal atrophy.

Screening for *depression* should be performed during the evaluation of all patients with cognitive symptoms or complaints both because patients with depression may present with memory complaints and because patients with neurodegenerative disease frequently have comorbid depression that contributes to poor cognition. In contrast to patients with neurodegenerative disease who often lack insight into their forgetfulness and frequently confabulate, patients with depression are frequently concerned about memory loss. In depression, bedside neuropsychologic testing classically reveals deficits in memory retrieval with associated mild deficits in attention in addition to the affective disorder.

Obstructive sleep apnea is another important cause of cognitive disturbances. The excessive daytime sleepiness that occurs reduces the ability to focus sustained attention and results in executive and memory dysfunction. In addition, sleep apnea is a risk factor for cerebrovascular disease and stroke, which can augment cognitive decline over time. Effective screening for the sleep disorder includes asking bed partners about snoring and querying the patient about daytime sleepiness; positive screening should trigger a referral for overnight polysomnography.

SYSTEMIC COMPLICATIONS OF DEMENTIA

Patients with dementia are vulnerable to a number of systemic complications (Table 62-2). These complications, especially aspiration leading to pneumonia and falls resulting in hip fracture, are often the cause of death in patients with advanced dementia. Familiarity with these complications of dementia will help providers caring for this population of patients anticipate and, in some cases, prevent these problems.

Dysphagia and Aspiration

Dysphagia occurs in up to half of patients with dementia.[8] In the setting of dementia, the neuroanatomic basis of dysphagia is complex and poorly understood. It tends to occur at earlier stages in the synucleinopathies and Alzheimer disease than in frontotemporal dementia. Dysphagia results in decreased oral intake, malnutrition, dehydration, and is a significant risk factor for aspiration

TABLE 62-2 ■ Systemic Complications of Dementia and Neurodegenerative Disease

Neurodegenerative Disease	Common Systemic Complications
Alzheimer disease	Agitation/delirium Dysphagia/aspiration Falls
Vascular dementia	Falls Depression
Parkinson disease	Dysphagia/aspiration Falls Orthostatic hypotension Excessive daytime sleepiness REM sleep behavior disorder Fatigue Constipation Depression
Dementia with Lewy bodies	As with Parkinson disease, plus: Agitation/delirium Hallucinations and sensitivity to antipsychotics
Multiple system atrophy	As with Parkinson disease, plus: Urinary incontinence Sleep-disordered breathing (sleep apnea, stridor, central hypoventilation)
Frontotemporal dementia	Motor neuron disease
Progressive supranuclear palsy	Falls
Corticobasal syndrome	Falls

REM, rapid eye movement.

of oral contents and resultant pneumonia, which is a common cause of death among the demented elderly. This raises two important questions: can aspiration and aspiration pneumonia be prevented, and how should families of demented patients be counseled regarding the risk and outcome of recurrent aspiration?

Aspiration occurs when food or saliva penetrates the trachea beyond the level of the true vocal folds due to incomplete or delayed closing of the epiglottis during the act of swallowing. During swallowing, the hyoid muscles contract and elevate the larynx, causing the epiglottis to seal the opening to the trachea and allowing oral contents to pass safely into the esophagus. Neurologic disease can cause aspiration due to lesions in the cortex, brainstem, cranial nerves, neuromuscular junction, or muscles that results in incoordination, slowness, or weakness of the swallowing mechanism. In dementia, one theory is that dysphagia is due to disruption of the cortical control of swallowing, causing apraxia and tactile-oral agnosia. Synucleinopathies may disrupt brainstem swallowing networks and cause dysphagia; α-synuclein is also found in sensory neurons in the region of the esophagus critical for initiating the deglutition reflex, suggesting a more local effect. Dysphagia and aspiration occur more typically with liquids than with solids in neurologic disease because liquids enter the posterior oropharynx more quickly and require more complete closure of the trachea and a more rapid swallow mechanism.

Patients with dementia should be routinely screened for symptoms of dysphagia, not only to predict and prevent aspiration, but also to assess nutritional status and quality of life with respect to eating. Clinical signs of dysphagia that are most predictive of aspiration include dysphonia and a wet voice or cough after a trial of swallowing 10 ml of thin liquid. An episode of pneumonia in a nursing-home patient is a likely indication of dysphagia and aspiration. When aspiration is suspected, patients should be referred to a speech and swallow therapist to assess the risk of aspiration through a formal dysphagia evaluation that could include a videofluoroscopic swallowing examination or a flexible endoscopic evaluation of swallowing. In addition, the therapist can recommend dietary modifications or swallowing techniques that may lessen the risk of aspiration.[8]

Dietary modifications to reduce the frequency of aspiration consist of thickening liquids to a nectar- or honey-thick consistency to allow the poorly coordinated swallowing mechanism time to function effectively by slowing the passage of oral contents from the posterior oropharynx into the esophagus.[8] The honey-thick consistency is more effective than nectar-thick consistency in reducing aspiration risk compared with thin liquids, but neither reduces the incidence of pneumonia in patients with dementia and Parkinson disease.[8] The chin-tuck, in which patients swallow with their chin touching their chest, also reduces the risk of aspiration but not pneumonia, and, while less effective than thickened liquids, it is preferred by patients. Practical challenges to these interventions include the supervision required to remind patients with dementia about proper swallowing technique and an increased risk of dehydration with thickened liquids.

Observational studies have not shown percutaneous enteral feeding tubes to reduce rates of pneumonia or prolong survival in patients with dementia, although no randomized trials have been conducted.[9] There are even more limited data on the effect of nasogastric feeding tubes on quality of life.[9] Patients with dementia in whom tube feeding is considered are often at the end-stages of their disease; among nursing home residents with advanced dementia, the 1-year mortality after feeding tube insertion was 64 percent in a study of United States Medicare and Medicaid beneficiaries. In another study, median survival after feeding tube insertion was 177 days.[9] In the absence of disease-modifying treatment or a clear benefit of tube feeding, the utility of this intervention in patients with dementia has been questioned. Despite this, approximately one-third of nursing home residents with dementia in the United States have feeding tubes.[9]

Tube feeding may not alter the risk of aspiration pneumonia and mortality in part because dysphagia is not the only risk factor for pneumonia among frail elderly patients. Restricting patients' oral intake does not prevent aspiration of saliva or regurgitated stomach contents. In addition to dementia, other risk factors for pneumonia include pre-existing lung disease, congestive heart failure, diabetes, malnutrition, bad oral health, and poor functional status. Proton pump inhibitors and histamine receptor antagonists are also risk factors for development of pneumonia.

Placement of an enteral feeding tube therefore requires careful discussion with patients and their caregivers, with all parties having a full understanding of the intervention's uncertain benefit in patients with dementia. Because patients with dementia in whom a decision about enteral feeding is being made often lack decision-making capacity, the responsibility for the decision may fall on surrogate decision-makers who struggle with a perceived dichotomy of providing or withholding nutrition. If patients have not made their wishes clear in advance, this can be a difficult position for surrogates. Reframing the decision to include the option of comfort feeding, which consists of hand feeding with the goal of comfort only, can provide caregivers with an acceptable option in which feedings are still being provided despite the risks of aspiration, but the potential harms of a feeding tube are avoided.[9]

Agitation and Delirium

Demented patients sometimes display aggressive or irrational behavior. Because of the practical challenges in managing such behavior and the emotional burden of seeing a loved one act in a manner incongruent with their usual personality, this can be one of the biggest challenges faced by caregivers of demented patients. Agitation may occur in the setting of delirium or it may be a feature of the dementia itself. Delirium is an acute alteration in mental status with a fluctuating course, impaired attention, and disorganized thinking or an altered level of consciousness in which patients are sometimes somnolent and relatively docile but can also be hypervigilant, impulsive, difficult to redirect, and combative.

Delirium is a common complication of dementia in hospitals, nursing homes, and the community. At least 50 percent of patients with dementia become delirious when hospitalized, and delirium is a common reason dementia patients present to the emergency department.[10] After an episode of delirium resolves, patients with dementia often do not return to their albeit impaired premorbid level of cognitive and physical function, and may experience an accelerated trajectory of cognitive decline.[10] Patients hospitalized with delirium superimposed on dementia have a fivefold increased mortality rate compared with demented patients hospitalized without delirium, and also experience longer lengths of hospital stay and increased rates of institutionalization, highlighting the need for delirium prevention, early detection, and treatment.[10]

Although delirium superimposed on dementia may occur without a specific trigger, there are a number of iatrogenic, metabolic, and systemic derangements that can precipitate an episode of delirium. In such cases, the delirium will not resolve until the underlying problem is diagnosed and treated. Medications are perhaps the most frequent iatrogenic precipitants of delirium. Polypharmacy as well as specific medication classes such as opiates, benzodiazepines, and anticholinergics have been implicated. For this reason, the first step in the treatment of delirium is a thorough review of the patient's medication list, including prescription, nonprescription, and alternative medicines. Attention should be given to reducing doses, minimizing polypharmacy, and replacing neurologically active medications with alternatives. Systemic infections such as cystitis or pneumonia are also common causes of delirium in patients with dementia, as are uremia, hepatic disease, electrolyte and glucose disturbances, urinary retention, constipation, hip fracture, and major surgery.[10] Indeed, delirium may be the first sign of a metabolic problem or infection and should trigger a laboratory and infectious work-up. Hospitalization itself may precipitate delirium in dementia patients, due to the sudden relocation to an unfamiliar environment, sleep deprivation, and confinement to a hospital bed. For this reason, hospitalization of demented patients should not be undertaken lightly. In some cases delirium will only resolve when the patient is returned to their home environment.

Among patients with dementia, agitation and delirium often peak in the afternoon and evening, a phenomenon known as "sundowning." The pathophysiologic basis of sundowning is not clear. It is theorized that degeneration of neurons involved in circadian rhythms in both the suprachiasmatic nucleus and the basal forebrain underlie the development of this time-dependent behavior.

Strategies to prevent delirium differ slightly between the hospital and the nursing home or community setting. In the hospital, multicomponent nonpharmacologic interventions have been demonstrated in randomized trials to lower the incidence of delirium; no medications are known to reduce delirium among hospitalized demented patients. Patients with cognitive impairment are frequently reoriented, and visits with volunteers and family members involve structured reminiscence. Maintenance of a normal sleep–wake cycle is achieved by minimizing night-time interruptions for vital signs and diagnostic tests, avoiding daytime naps, providing cognitive stimulation and mobilization throughout the day, and keeping the hospital ward quiet at night. Sensory deprivation is minimized by providing hearing aids, portable amplifying devices, corrective lenses, and adaptive equipment such as telephones with large keypads for those with impaired vision. Tethers such as restraints and bladder catheters are carefully avoided. Attention is paid to maintaining hydration orally, and patients are monitored and treated for hypoxemia, constipation, and urinary retention. Meta-analyses demonstrate that the odds of delirium can be reduced by at least 40 percent with these interventions, and this multicomponent approach is recommended in several guidelines.[10]

When delirium does occur in the hospital, the initial focus should be on diagnosing and treating the underlying cause, if found. The same nonpharmacologic measures effective in preventing delirium should be employed to treat it. Pharmacotherapy should be reserved for situations in which patients pose a danger to themselves or to the hospital staff. If medications must be administered, the initial choice should be an antipsychotic at the lowest dose possible, and prescribers should recognize the medication is being used as a sedative and not as a treatment for delirium. However, these agents must be used with caution because they are associated with an increased risk of death in the elderly and are not approved by the United States Food and Drug Administration for this indication. Antipsychotics are also especially dangerous in dementia with Lewy bodies and should be avoided due to the possibility of precipitating a rapid and sometimes permanent encephalopathy and rigid state, even in low doses. Benzodiazepines should be avoided except in cases of alcohol withdrawal delirium.

Outside the hospital setting, agitated and aggressive behavior is less often the result of an acute metabolic or infectious problem—although these triggers should never be overlooked—and more often the result of the neurodegenerative process itself or sundowning. In this setting, interventions are aimed at reducing the incidence and severity of agitated outbursts and deescalating aggressive behavior. Both pharmacologic and nonpharmacologic measures have been studied.

Pimavanserin, a serotonin (2A) agonist, is approved by the U.S. Food and Drug Administration for the treatment of hallucinations and delusions in patients with Parkinson disease, but not for the treatment of agitation. There are no approved treatments for aggressive behavior in patients with dementia of any cause. Citalopram, a selective serotonin reuptake inhibitor, demonstrated a modest reduction in agitation among patients with Alzheimer disease in a single randomized trial; notably, cognition worsened with treatment.[2] Atypical antipsychotics are the most widely studied medications for the prevention of agitation in patients with dementia. Meta-analyses of randomized controlled trials found risperidone, aripiprazole, and olanzapine effective in reducing psychotic symptoms and aggression in Alzheimer disease.[11] Risperidone and olanzapine also reduced caregiver burden. Of concern, however, is the finding that atypical antipsychotics increase the risk of death in patients with dementia, likely mediated by an increased incidence of cardiovascular and cerebrovascular events and pneumonia. Antipsychotics also increase the risk of extrapyramidal side effects and accelerate cognitive decline and can dramatically worsen cognition in patients with Lewy body dementia. The use of atypical antipsychotics for behavioral modification in dementia should therefore be reserved for cases where agitation poses a risk to the safety of the patient or caregiver. In such cases, careful documentation of the consent process is important. Antipsychotics, pimavanserin and citalopram can all prolong the QTc interval, which must be monitored periodically. Cholinesterase inhibitors are not effective for prevention of agitation in Alzheimer disease, but are helpful in dementia with Lewy bodies.[11]

Nonpharmacologic prevention of agitation at home and in the nursing home setting focuses on behavioral techniques aimed at anticipating and avoiding triggers, meeting unmet needs, diffusing aggressive behavior, and minimizing caregiver upset. Several randomized trials have examined caregiver training and support strategies and demonstrate greater improvements in problem behaviors and caregiver well-being than atypical antipsychotics.[11] While these types of interventions show promise and lack the risks of pharmacotherapy for agitation in dementia, nonpharmacologic methods require significant investment in human resources without a clear financial incentive and have received less attention and research funding to date.

Depression and Other Mood Disorders

Comorbid mood disorders are highly prevalent among patients with dementia. It is estimated that at least 20 percent of patients with Alzheimer disease have comorbid depression, and rates are even higher in Parkinson disease.[2] Anxiety is also common in neurodegenerative diseases.

Depression has also been identified as a risk factor for dementia in multiple cohort studies, but it is not clear whether depression represents a prodromal phase of dementia, the consequence of dementia, or a modifiable risk factor.[2] Several studies finding a two- to fourfold increased risk of developing dementia later in life among patients with depression in their youth or middle age support the hypothesis that early or midlife depression is a potentially modifiable risk factor.[2]

Among patients with dementia, data regarding treatment of depression are limited. Psychologic therapy employing techniques used in patients with depression without dementia may have a small effect and can be attempted.[2] Randomized trials have not demonstrated efficacy of antidepressants in patients with dementia, although selective serotonin reuptake inhibitors are nevertheless frequently prescribed in this setting.[2] Given their lack of proven efficacy, however, they should be prescribed with caution and patients should be carefully monitored for adverse effects.

Falls

Falls are an early feature of some dementias and a late feature of others. The parkinsonian syndromes are all characterized by early falls due to axial rigidity and loss of postural reflexes resulting in postural instability. In PSP, the inability to look down because of the supranuclear gaze palsy from which the disease's name is derived is an additional exacerbating factor. In other dementias, while postural instability due to the neurodegenerative disease may contribute to falls, the cause is often multifactorial, with additional risk factors including dizziness, lower extremity weakness, visual impairment, polypharmacy, orthostatic hypotension, and a home environment that is not optimized for elder living.

Falls are a dangerous and much-feared event for patients with dementia and their caregivers. A fall leading to a broken hip often leads to the end of independent living and carries a high mortality rate. It is estimated that the probability of falling within 1 year among patients older than 65 years is 19 to 36 percent; this figure is higher in patients with dementia.[12] For this reason, fall prevention is an important part of the care of elderly demented patients.

The most important factor that predicts future falls in older adults is a prior fall within the past year, with positive likelihood ratios of 2.3 to 2.8.[12] Among patients who have not fallen, subjective and objective assessment of gait and balance is likely the most efficient means of screening for those at highest risk. A self-perceived mobility problem has a positive likelihood ratio of 1.7 to 2.0; objective assessments revealing an inability to stand for 10 seconds while keeping the heel of one foot touching the toe of the other, an inability to tandem walk, and taking more than 13 seconds to walk 10 meters, each have positive likelihood ratios of 2.0 to 2.4.[12] For inpatients, the risk of falls can be assessed using one of several tools, including the St. Thomas Risk Assessment Tool in Falling Elderly Inpatients, the Morse Fall Scale, and the Hendrich Fall Risk Model. Factors predictive of inpatient falls using these tools include a history of recent falls, agitation, visual impairment, the need for frequent toileting, requirement of an aid for ambulation, and gait impairment.

Among community-dwelling elderly adults, the risk of falling can be reduced by roughly 25 percent with multifactorial prevention interventions, especially if the interventions include an exercise program that targets balance, gait, and strength.[13] These interventions typically include a risk assessment that reviews medications; assessment of basic and instrumental activities of daily living; measurement of orthostatic blood pressure and visual acuity; evaluation of gait, balance, and cognition; and a detailed assessment of home safety. This risk assessment is followed by targeted interventions that may include elimination of high-risk medications (such as antipsychotics and other potentially sedating medications), a physical therapy or exercise program, education of patients and caregivers, and home safety improvements. In the inpatient setting, falls can be prevented with the same multicomponent intervention designed to prevent delirium.[10]

Orthostatic Hypotension

Postural hypotension is a common complication of certain dementias, especially synucleinopathies. Patients with these disorders should be assessed for this condition when presenting with low blood pressure, dizziness, or falls. Assessment and treatment of postural hypotension are discussed in Chapter 8.

Sleep Disorders

Disturbances of sleep are common among patients with dementia. Some disorders, such as sundowning and insomnia, are common to all forms of dementia, whereas others appear unique to the synucleinopathies. This predilection may be due to the predisposition of α-synuclein aggregates to affect brainstem neurons and interrupt projections involved in arousal and modulation of tone during sleep.

REM sleep behavior disorder is a condition common to the synucleinopathies in which patients act out their dreams during REM sleep. During REM sleep, pathways descending from the lower brainstem to the spinal cord normally cause atonia. It is hypothesized that degeneration of these descending fibers allows uninhibited flow of cortical signals generated during dreams to cause muscle activation. The movements associated with REM sleep behavior disorder are dramatic; often patients have to stop sleeping with their bed partner in consequence. The sleep disorder may precede the development of other manifestations of a synucleinopathy by many years, and approximately 80 percent of patients with REM sleep behavior disorder will develop a synucleinopathy if followed for 10 or more years.[14] Clonazepam taken 30 minutes before bedtime is often effective in treating REM sleep behavior disorder but may cause excessive daytime sleepiness, sleep apnea, behavioral disorders, and unsteadiness, especially in demented patients; melatonin at doses of 3 to 9 mg in the evening has also been helpful in nonrandomized studies.[14] Medications that cause REM sleep behavior disorder, such as selective serotonin reuptake inhibitors, should be discontinued.

Large cohort studies suggest 40 to 50 percent of patients with Parkinson disease suffer from excessive daytime sleepiness, with smaller studies finding similar rates among patients with dementia with Lewy bodies.[4,15] Daytime sleepiness can be exacerbated by the use of the dopamine agonists ropinirole and pramipexole, but it occurs in Parkinson disease independently of medications as well.[15] Fatigue is also a common symptom in Parkinson disease and is more highly correlated with depression than sleepiness, but often occurs independently of both. The degree of daytime sleepiness can be assessed using the Epworth Sleepiness Scale. Treatment for excessive daytime sleepiness should start with education on sleep hygiene in order to reduce insomnia. Patients should be screened for sleep apnea and referred for a sleep study if appropriate. Unfortunately, studies of stimulants such as modafenil, methyphenidate, and caffeine have not demonstrated efficacy in reducing either excessive daytime sleepiness or fatigue in Parkinson disease.[15]

Excessive daytime sleepiness occurs at a similar frequency in multiple system atrophy as in Parkinson disease, but it is correlated with a higher incidence of sleep-disordered breathing.[5] Sleep-disordered breathing in multiple system atrophy manifests as obstructive sleep apnea, nocturnal stridor, and central hypoventilation and is an important condition for clinicians caring for these patients to recognize.[5] These disorders may also occur in other synucleinopathies but do so less frequently. Stridor is due to dystonia of the vocal cords and can result in airway obstruction; it is a risk factor for shortened survival in multiple system atrophy. Treatment with continuous positive airway pressure (CPAP) or botulinum toxin injections to the vocal folds, guided by electromyography, may be successful. Tracheostomy may be necessary in cases where stridor occurs during wakefulness or CPAP is not tolerated, although sudden death may still occur due to central hypoventilation.

Gastrointestinal and Genitourinary Complications

Constipation is a prominent feature of the synucleinopathies.[5,15] Its cause may be disruption of parasympathetic efferents by α-synuclein pathology in the brainstem, dysfunction of the enteric nervous system due to α-synuclein accumulation in myenteric plexus, or a combination of both.[15] Treatment consists of osmotic laxatives such as macrogol, the prosecretory locally acting chloride channel activator lubiprostone, and probiotics combined with prebiotic fiber.[15]

Incontinence is common in end-stage dementia. In most dementias, the mechanism of incontinence is one of impaired central inhibition, due to involvement of either pontine or forebrain micturition centers, resulting in urge incontinence. This is in contrast to multiple system atrophy, in which a neurogenic bladder with large postvoid residuals and overflow incontinence is the rule as part of a more systemic autonomic neuropathy. There are few studies of nonpharmacologic management of urinary incontinence in dementia; among these, timed and prompted voiding may be of benefit. Anticholinergic medications should be used with caution given the risk of precipitating delirium in elderly patients with dementia. Bladder catheters should be avoided because they increase the chance of infection and provide a tether to the patient's bed, thereby decreasing mobility and increasing the risk of delirium.

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CHAPTER

63

Care at the End of Life

MICHAEL J. AMINOFF

PHYSICIAN–PATIENT INTERACTIONS
PROVISION OF CARE
SPECIAL NEUROLOGIC CIRCUMSTANCES
  Persistent Vegetative and Minimally Conscious States
  De-efferented State
  Advanced Dementia
  Amyotrophic Lateral Sclerosis
CONCLUDING COMMENTS

Neurologic disorders are often progressive, may be incurable, and commonly lead to significant disability. Palliative care is an important aspect of their management and may be required at any stage of the disease process. This chapter focuses on one specific aspect of palliative medicine, namely end-of-life care, which is often inadequate even in advanced societies.

With the advent of increasingly sophisticated technology and more powerful pharmacologic agents, it has become possible to prolong the last stages of life in patients with severe and irreversible medical disorders, in whom a long-term favorable outcome cannot be achieved. In some instances, the futile use of sophisticated technology to maintain certain bodily functions in individuals with no prospect of useful recovery has involved major financial outlay, an added burden on patients in advanced stages of incurable disease, and unnecessary and prolonged emotional distress to relatives and friends. Indeed, impersonal advances in modern medicine have led to increasing indignity and fear in many individuals as the end of life draws near, and some will die with unrelieved and uncontrolled symptoms.

Neurologists are often required to look after patients at the end of life either because a primary neurologic disorder reaches a terminal phase or because patients with primary medical disorders develop a catastrophic neurologic complication leading to consultation. The ability to recognize the last hours or days of life, that is, to diagnose “dying,” is an important clinical skill that is a prerequisite to the provision of appropriate care.[1] Such patients are usually obtunded, able to take only sips of fluids, unable to take oral medications, and unresponsive to modifications in their therapeutic regimen; there may be no obvious reversible precipitant of their deterioration. Patient management is optimized when there is agreement between members of the healthcare team that the patient is indeed dying.[1] In this circumstance, it is important to avoid giving conflicting messages to patients and their families about the likely course of events.

PHYSICIAN–PATIENT INTERACTIONS

It is the responsibility of all physicians to provide adequate care for patients who have a terminal disease or are dying. The focus of care changes from attempts to reverse or cure an underlying disease to providing compassionate and sensitive care for patients facing imminent death. Such care may be required for no more than a few hours or for as long as several months, depending on the nature of the underlying disorder. Patients or their surrogates will need to be informed of the severity of their disease, and—depending on the circumstances—this is generally best accomplished gradually and with

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sensitivity, bearing in mind what they do (and do not) want to know. Patients want hope and reassurance—not necessarily that they will live but that there are options to help their isolation, fear, physical discomfort, and mental distress. Physicians must assume responsibility for helping patients to deal with the bleak uncertainty of the future and to cope with the sense of isolation and dependency that is often experienced with the approach of death. Fears concerning pain or discomfort can often be alleviated by proper explanation, and supportive care by family, friends, and medical attendants may help to diminish otherwise overwhelming feelings of isolation and uncertainty. Some physicians still feel a certain guilt or responsibility for the death of patients, and this colors their approach to patients who are dying. Such attitudes will change only with the wider appreciation that death is but a natural milestone.

With the increasing emphasis on the scientific aspects of modern medicine, the art of the discipline—its human side—is often overlooked. Physicians must be prepared to spend time with their patients to provide support, education, and adequate symptomatic relief and to work with them and their family to enable them to come to terms with events. Unfortunately, however, such discussion and resultant decision-making substantially in advance of death are uncommon. The demands on physicians by patients may be considerable as death approaches. It is especially important for physicians to understand the needs of patients who are unable or unwilling to communicate with them. Patients need to know that they will continue to receive support and care from their physician throughout the process of dying. A cursory glance at patients during the course of a busy ward-round is quite inadequate in this regard. Patients may worry especially if they are to be moved from their home to a hospital, or from one medical facility to another. It should therefore be stressed that they are not being abandoned, that their care will be coordinated and continuity of care assured.

The family, also, may require considerable attention from physicians. This requires a sensitivity to their needs and the ability to communicate fully with them at all times, providing adequate responses to their queries; meeting with them after death has occurred often helps to settle unresolved fears and concerns. The care of terminally ill patients and their families usually requires the cooperation of the entire healthcare team, including nursing staff, social workers, physical and occupational therapists, respiratory therapists, dieticians, and psychotherapists, as well as physicians. The spiritual needs of the family must not be overlooked, and the clergy have an important role in this context.

In many countries, the general public has expressed increasing dissatisfaction with the care received by people who are dying. Fueled by concerns about the quality of end-of-life care, support has grown for the concept that patients with terminal illnesses should have the right to request assistance in dying. The extent to which physicians can assist in this regard is governed by national statutes, and the extent to which physicians choose to become involved in this context is personal and individual. Regardless, many individual physicians support the legalization of medically assisted suicide and voluntary euthanasia, although numerous professional organizations oppose such an approach. Medically assisted suicide involves providing the means for patients intentionally to kill themselves, whereas voluntary euthanasia consists of the deliberate killing of patients at their request. The provision of appropriate palliative care for dying patients would make such radical alternatives unnecessary in many instances. Pain relief, for example, must be adequate even if, as an unintended side effect, the medications used to control pain lead to some shortening of life in consequence.

Ethicists and educators have emphasized patient autonomy in the decision-making process. However, in a study of 8,308 hospitalized patients, 67 percent ultimately preferred to leave medical decisions to their doctor, even though 97 percent wanted their physician to offer them therapeutic choices and consider their opinions.[2] Thus, both patient autonomy and physician beneficence remain important in guiding clinical care. Some patients with advanced medical disease may seek a particular therapeutic intervention that seems unjustified to their physician. Clinicians should behave in a manner that does not conflict with their own beliefs; if differences with patients and their families cannot be resolved by discussion and explanation, it is sometimes worthwhile to transfer patients—with their consent—to the care of another physician. Physicians have the responsibility of withholding treatment when the distress or other adverse effects of therapy cannot be justified by unrealistic hopes of curing or arresting the underlying medical disorder and of withdrawing life-prolonging maneuvers when these have become too burdensome for patients.

Competent adults have the right to refuse medical treatment or to request its discontinuation. Despite this, many patients dying in hospital continue to receive unwanted interventions such as intensive life support that postpone death. Patients' refusals of supportive measures often signify no more than a wish to do without the burden of life-sustaining medical treatment rather than a wish to die. The goals of such treatment must constantly be reappraised by patients, relatives, and medical staff. Even routine procedures such as radiographs, blood tests, and respiratory care may become unwelcome and tiresome interruptions during the last days of life, and the need for them must be re-evaluated as the patient's condition deteriorates. When patients do refuse treatment, however, physicians are responsible for ensuring that this is not an impulsive decision but is based on an understanding of the implications of such a choice.

For competent patients to make informed decisions, it is important that they are properly educated by their physician about their prognosis and options. They should also be encouraged to use advance directives such as a living will to ensure that their own wishes regarding medical intervention are followed if they later become unable to express their preferences because of physical or mental limitations. Such directives should be reviewed and updated regularly. A durable power of attorney for health care in the United States gives another person the power to make medical decisions for the patient as necessary. It is important that physicians educate patients about such opportunities and the ability to make advance directives. Physicians also must be able to assess a patient's competence to make decisions and properly inform proxy decision-makers about the patient's disorder, therapeutic options, and prognosis. Proxies are generally expected to make decisions based on what the patient would have wished, and this assumes some knowledge of the patient's preferences (the substituted judgment standard). Without such knowledge, the proxy can only balance the benefits of any treatment or course of action against the possible burdens (the best interests standard). When the perceived benefits are greater, consent is provided; if the likely burdens exceed any potential benefit, consent is refused.

However, there is a discrepancy between theoretical ethical concepts and clinical reality. A study of dialysis patients revealed that many would allow their designated surrogate to override their advance directives if this was in their interests. Another study found that many elderly or seriously ill hospitalized patients (more than 70%) would not want their stated resuscitation preferences to be followed if they were to lose decision-making capacity but preferred that their family and physician make such decisions for them.[3] It seems that proxy decision-makers have the discretion to assess novel and perhaps unforeseen circumstances, make moral judgments, and sometimes make decisions that differ from the patient's original intent; for example, because the patient's wishes cannot be applied in certain clinical contexts.[4]

When patients do not have the capacity to make clinical decisions and have no designated surrogate, many states allow a next-of-kin surrogate to be appointed. Decisions by both patient-designated and next-of-kin surrogates are prone to error. A systematic literature review and analysis of 16 eligible studies involving 151 hypothetical scenarios and 2,595 surrogate–patient pairs, which collectively analyzed 19,526 patient–surrogate paired responses, showed that surrogates predicted patients' end-of-life treatment preferences with only 68 percent accuracy.[5] Surrogates were least accurate in scenarios involving stroke or dementia. Surprisingly, accuracy was not improved when the patient had designated the surrogate or by prior discussion between patients and surrogates about treatment preferences. Nevertheless, surrogates were more accurate than physicians in predicting patients' treatment preferences.

To better understand the moral obligations of the patient–proxy relationship, Fins and colleagues surveyed 50 patient–proxy pairs and 52 individuals who had been proxies for someone who had died.[4] They used structured vignettes of three separate diseases (one of which was acute stroke), and examined whether respondents believed that proxies should follow explicit instructions and thus act contractually regarding life-sustaining therapy or whether more discretionary (or covenantal) judgments were acceptable. Other variables included the "valence" of initial patient instructions (e.g., "to do nothing" or "to do everything") and the quality of information available to the proxy. They found that the patient–proxy relationship exists on a contractual to covenantal continuum and that disease course, the clarity of prognosis, instructional valence, and quality of patient instructions led to response differences. The use of interpretative or covenantal judgment was desired by patients and proxies when the prognosis was grim, despite initial instructions to pursue more aggressive care. When hopeful feelings modified initial negative instructions, proxies were more uncertain about the propriety of doing nothing.

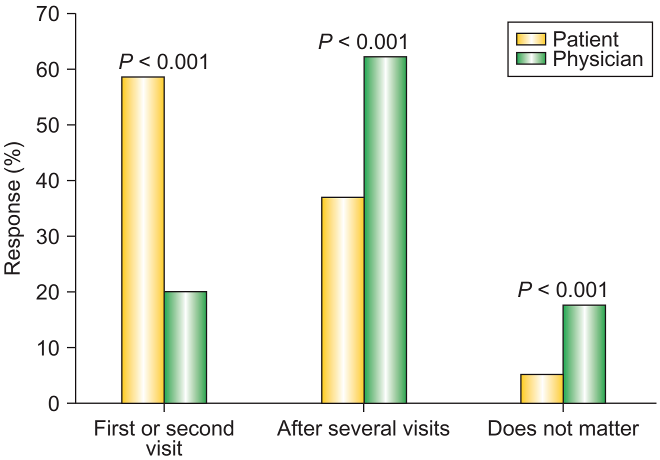

FIGURE 63-1 ■ Patient and physician opinions regarding when advance directives should be discussed. (From Johnston SC, Pfeifer MP, McNutt R, for the End of Life Study Group: The discussion about advance directives. Patient and physician opinions regarding when and how it should be conducted. Arch Intern Med 155:1025, 1995, with permission.)

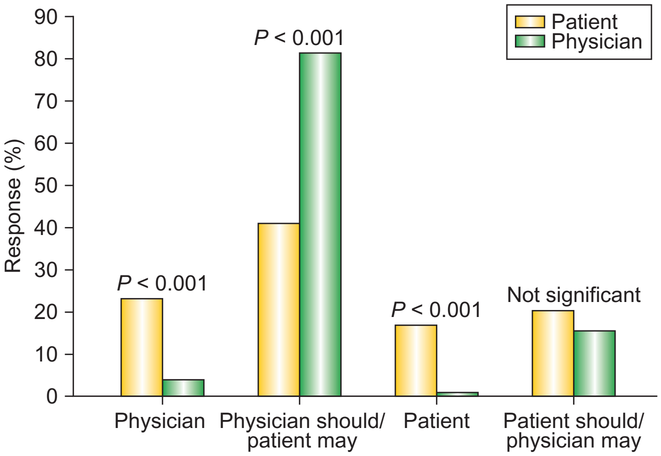

FIGURE 63-2 ■ Patient and physician opinions about who should initiate discussion about advance directives. (From Johnston SC, Pfeifer MP, McNutt R, for the End of Life Study Group: The discussion about advance directives. Patient and physician opinions regarding when and how it should be conducted. Arch Intern Med 155:1025, 1995, with permission.)

Nonetheless, patients and proxies intended that negative instructions to be left alone should be heeded. Respondents did not adhere to narrow notions of patient self-determination but made nuanced and contextually informed moral judgments that were not viewed by patients or proxies as violations of the principal's autonomy. Although respondents were better educated than the general public and were restricted to self-identified English-speaking Americans of European origin (to avoid the possible confounders of race and ethnicity), these data suggest that advance-care planning should consider both the exercise of autonomy and the interpretative function assumed by the proxy.[4]

Studies have indicated that patients want to discuss advance directives earlier than their physicians and before they are "extremely ill" (Fig. 63-1). Most believe that such discussion should occur when they are still healthy. Both patients and clinicians believe that it is the physician who should initiate the discussion (Fig. 63-2), but physicians are often reluctant or fail to do so, being concerned that they will upset or worry patients. In consequence, a crisis may lead to unplanned and unwanted interventions. Many patients believe that others (e.g., a spouse or "significant other," children, or parents) should be brought into the discussion. Most also believe that it should occur before hospitalization and over several visits. In such discussions, physicians must allow patients to speak uninterrupted and respond sympathetically, with kindness and in simple neutral terms, avoiding jargon or technical terms that may not be understood. The importance of imparting accurate prognostic information was mentioned earlier.

Many healthy subjects consider certain neurologic states to be unacceptable and express the belief that they would not want to remain alive in those circumstances. However, after developing such disability, some patients change their opinion and may experience a better quality of life than previously envisioned, as discussed later with particular regard to the de-efferented state. This possibility must be borne in mind when statements made by a patient before their illness are considered.[6]

Decisions about whether to adopt life-sustaining measures often need to be made in a context where the prognosis is uncertain. It is important to note, however, that such decisions can be changed later as the prognosis becomes clearer because no logical or ethical distinction exists between withholding and withdrawing life-sustaining measures.

For patients nearing the end of life, decisions have to be made about whether cardiopulmonary resuscitation should be attempted, if the need arises. In patients with terminal diseases, such decisions often bear more on the issue of how a patient will die than on whether death will occur, and it is important for patients and family members to understand this distinction.

A decision by a patient (or family members) needs to be made in advance, so that individual wishes can be taken into account in the event that resuscitation is required. In many European countries, physicians take an active role in advising patients and family members about the most appropriate course of action to follow, whereas many physicians in the United States believe that this is an individual decision that is best left to the patient. It is this author's view that the physician—as the most informed person in the healthcare team—should be responsible for ensuring that the patient or surrogate is sufficiently well educated about the issues to make informed decisions, guided by suggestions or recommendations when these are requested of the medical staff.

It is often helpful to discuss the possibility of organ donation with dying patients when this is a significant consideration. This makes it easier for family members, who may otherwise have to be approached about the issue shortly after the death of their relative. A variety of ethnic, religious, and cultural factors affect attitudes concerning organ donation, and these must be respected. Physicians must appreciate that patients are not obliged to donate organs and may choose to limit any donation that they make.

PROVISION OF CARE

With their increasing emphasis on surgery and advanced technology, hospitals no longer are able to provide for the long-term care of patients who are dying. By contrast, the needs of the terminally ill are often met more fully in the environment of a hospice, where a multidisciplinary team can focus on their care and support, or at home, if an adequate family structure and medical/paramedical support are available. Hospice care can also be provided to patients in their own home, with comprehensive services offered to ensure patient comfort and provide help for the family in coping with the burden placed on them. Care for patients in a home environment requires careful education of the family, reduction of probable causes of stress (such as violence, agitation, or incontinence), support of caregivers by ensuring assistance from other ancillary healthcare providers, and provision of periodic respite to the family.[7] The interests of patients nevertheless remain the prime concern. When family members appear preoccupied more with their own welfare than that of a severely demented or dying patient, the possibility of patient abuse may require consideration.[7] Abuse of the weak or elderly is becoming an increasing problem and a matter of grave public health concern.

The care of terminally ill patients should be focused on improving the quality of life rather than simply on extending the duration of life. The aim is to ensure that patients are as comfortable as possible, even during the process of dying. The emphasis is thus on the control of symptoms. Pain is the most common symptom in dying patients. Pain, discomfort, distress, fatigue, dyspnea, anorexia, nausea, vomiting, cognitive disturbances, and affective disorders all require particular care. When the ability of patients to communicate is impaired, it is necessary to infer the presence of distress by such signs as agitation, restlessness, tachypnea, and tachycardia and to initiate treatment accordingly. Many patients fear that any later inability to communicate their distress will lead to unnecessary and increased suffering. The relatives of dying patients frequently complain that signs of distress were ignored in patients unable to communicate their needs verbally. No justification exists for limiting symptomatic measures in such circumstances; overtreatment is preferable to undertreatment.

Opioids have an important role in providing pain relief when nonopioid analgesia is inadequate. Morphine is also particularly useful in relieving dyspnea, often in lower doses than is required for pain. The optimal dose is that providing adequate relief. When it is introduced for pain, morphine is best started in an immediate-release formulation. A starting dose of 5 to 10 mg every 4 hours is often adequate, but higher doses may be needed if patients have previously received another opioid, such as dihydrocodeine. A double dose at bedtime may also be helpful. Rescue supplements of morphine are necessary for "breakthrough" pain. The total daily dose of morphine should be titrated upward rapidly (e.g., by 30 to 50%) if pain relief is inadequate. Once pain is controlled, a modified-release preparation of morphine can be used. Side effects of morphine, especially nausea and constipation, may require concomitant treatment. Delirium resulting from opioid treatment may respond to substitution with an alternative opioid. It may be necessary to administer opioids by a nonoral route in patients with severe vomiting or dysphagia, those with intestinal obstruction or malabsorption, or those unable to comply with an oral regimen. Subcutaneous infusion of diamorphine may be used for pain control in dying patients. Anxiety, agitation, or delirium may respond to benzodiazepines or neuroleptic agents.

Large doses of sedatives and analgesics may have to be administered to relieve pain and distress during the withholding or withdrawal of life-supporting measures, but death is not necessarily hastened by such medication. Supportive therapy is important. Attention to the environment may be rewarding. The intensive care unit, with its harsh light, endless noise, monitoring and other equipment, and frequent alarms, is an overwhelming place that provides no respite for dying patients.

More than half of the deaths occurring in intensive care units occur after life-supporting measures are withheld or withdrawn. Withdrawal of ventilator support is often particularly distressing for both relatives and medical staff, even though this is ethically no different from limiting other therapeutic or supportive measures. Ventilator withdrawal may be accomplished by extubation or by "terminal weaning" (in which ventilator rate, positive end-expiratory pressure, or tidal volume is gradually reduced with the endotracheal tube in place). Regardless of the method used, patient comfort must be ensured, as must the family's perception in this regard. For conscious patients requesting sedation for ventilator withdrawal, Brody and colleagues recommend 2 to 4 mg of midazolam intravenously before withdrawal, and 5 to 10 mg of morphine by intravenous bolus for distress during weaning, followed by continuous infusion (50% of bolus dose per hour); in patients with tolerance to such agents because of prior use, higher doses are needed.[8] Others have used pretreatment with the equivalent of 15 mg per hour of intravenous diazepam or 15 mg per hour of intravenous morphine, increasing the dose as necessary to relieve dyspnea and anxiety, even to the point of unconsciousness if required and requested.

Neuromuscular blocking agents should be discontinued before withdrawal of ventilator support, and indeed probably in all dying patients, to allow verbal communication when this is otherwise possible and to permit signs of distress to be manifest so that appropriate treatment can be provided.[8] The masking of such signs by neuromuscular paralysis serves no useful purpose, and the inability to exhibit signs of distress in this context cannot be taken to imply that such distress is absent.

Attention must be devoted to nutrition, hydration, care of the skin, and sphincter function. The nutrition and hydration of dying patients require careful consideration. The points to consider include whether such support should be provided at all, the manner in which it is best provided, and patients' tolerance of any resulting discomfort, complications, or side effects. There are benefits of withholding nutrition and hydration to shorten life when other treatment is to be discontinued. The artificial provision of nutrition and hydration is a life-sustaining maneuver that does not differ from other maneuvers that supplement or substitute for normal bodily functions. Withdrawal of artificial nutrition and hydration, however, has particular emotional implications for the general public and many clinicians. Such a course therefore demands specific discussion with patients (when communication is possible) and family members, as well as with other members of the healthcare team who may be concerned. It is avoided by some clinicians who fear it will add to patients' discomfort. In fact, however, it is unlikely to lead to much additional distress, and by shortening life may actually limit further discomfort. When distress does follow withdrawal of nutrition or hydration, additional symptomatic measures are necessary.[8] Dryness of the mouth is often relieved by ice chips, glycerin swabs, or petroleum jelly lip balm; withdrawal of medication that may be exacerbating this symptom should also be considered. Mouthwashes may relieve poor oral hygiene, and antimonilial therapy is indicated for candidiasis, antiemetics for nausea, and opiates or benzodiazepines for restlessness or pain.[8]

Some patients develop a "death rattle" as air passes over retained secretions at the back of the throat. This may be distressing to relatives and medical staff. Glycopyrrolate (0.1 mg intravenously every 4 hours as necessary) or—in obtunded patients—atropine (1 or 2 drops of a 1% ophthalmic solution sublingually each hour) may help. Butyl scopolamine 20 to 40 mg/day orally can also be tried.

Thus, the focus is on comfort measures, and nonessential medications and interventions (such as blood tests, intravenous fluids, and the like) are discontinued. Relief of pain, agitation, respiratory difficulty, and other distressing symptoms is assured. There must be good communication with the patient, family, and primary medical practitioner, and the plan of care must be explained to them and understood. Attention should also be focused on religious and spiritual needs.

Various structured systems have been developed to facilitate care practices and monitor their results. The extent to which they improve care is not entirely clear. One such system, initially well regarded, was the Liverpool Care Pathway in the United Kingdom, but subsequent criticism led to a government review and the recommendation that it be phased out in favor of personalized care plans

SPECIAL NEUROLOGIC CIRCUMSTANCES

Palliative care is important for patients with acute stroke, whose needs are often poorly understood. It may also facilitate discussion about such difficult issues as fears of dependence, disability, and death. Symptomatic treatment and comfort measures can improve the quality of life of patients with advanced-stage chronic neurologic diseases such as Parkinson disease. The spouses and other family members of such patients are often exhausted, socially isolated, and without adequate support to help them through bereavement. Bereavement counseling may then help in the transition to a noncaregiver role.

Certain circumstances that are particularly likely to be encountered by neurologists merit brief additional comment here. Difficulties are particularly likely in circumstances in which diagnosis and prognostication are based on purely descriptive aspects of clinical status rather than more objective quantitative laboratory criteria, such as in the management of patients with disorders of consciousness. This requires physicians to be very specific about their limitations in predicting the outcome of certain neurologic catastrophes.

Persistent Vegetative and Minimally Conscious States

The persistent vegetative state is characterized by loss of awareness despite the presence of sleep–wake cycles. It occurs in patients with destruction of the cerebral cortex but preservation of brainstem function. Such patients may survive for prolonged periods if provided with nutrition and fluids. There is general agreement that they do not experience pain or suffering, based on the lack of any behavioral indications of distress and the presence of extensive cortical damage that destroys the substrate of consciousness. Life-prolonging medical treatment can be withdrawn from a patient in a persistent vegetative state when it is clear that this accords with the previously expressed wishes of the patient and the family concurs with the withdrawal of such support. In general, the provision of nutrition and hydration is not to be withheld when the patient's prognosis is uncertain; its withdrawal at a later date is, however, appropriate when it is clear that the patient's condition is hopeless, which usually requires the vegetative state to have persisted for at least 1 month. However, recovery from a vegetative state may take longer than this, depending in part on the underlying etiology.[9] Indeed, a vegetative state is generally required to last for more than 3 months after an anoxic injury or 1 year after a traumatic brain injury before it is considered permanent, and even then a slim chance remains of further recovery with time. Thus, decisions to remove life-supporting measures are commonly made while the likelihood and extent of recovery are uncertain and, consequently, may be influenced by the personal biases of treating medical and nursing staff. It is clearly appropriate in such a context to explain the prognostic dilemma to family members so that decisions are truly informed ones. Management problems may occur when the family is not of one mind about how to proceed. A case in point was that of Terri Schiavo, who was in a post-anoxic persistent vegetative state for some 8 years when her husband took legal steps—opposed by her parents—to remove her feeding tube and discontinue life-prolonging measures.[10] The resulting legal struggle continued over several years and involved various levels of the judiciary as well as state and federal legislative interventions, but support was eventually withdrawn and autopsy confirmed the presence of extensive, irreversible brain damage.

The so-called minimally conscious state designates a state in which patients exhibit inconsistent but discernible evidence of consciousness. It is thus quite distinct from the vegetative state, but it remains difficult to define. Some degree of functional recovery of behaviors suggesting self- or environmental awareness has occurred. Such behaviors may, for example, include basic verbalization or context-appropriate gestures (regardless of accuracy), appropriate emotional responses (e.g., smiling or crying) to the linguistic or visual content of emotional but not neutral stimuli, or more simple activities such as purposive behaviors in response to environmental stimuli (e.g., a finger movement or eye blink apparently to command) or pursuit eye movement or sustained ocular fixation in response to moving or prominent stimuli. Improvement from this state is demonstrated by the restoration of consistent functional communication with the patient.

The minimally conscious state may occur in different neurologic contexts in which there has been a loss of cerebral function and may be temporary or permanent. Only limited information is available about the natural history or long-term outlook, and it depends in part on the etiology of the underlying neurologic disorder. Thus, the prognosis is better for those in whom traumatic brain injury was responsible than in other instances. The likelihood of useful functional recovery declines with time, and patients remaining in a minimally conscious state for more than 12 months are likely to remain severely disabled and without a reliable means of communication, although well-publicized clinical exceptions exist. The patient Terry Wallis, for example, was in a post-traumatic minimally conscious state for some 19 years before recovering awareness and fluent speech, but then remained unaware of all that had transpired since his injury.[11] The clinical examination provides only limited help in defining the prognosis, and whether imaging and electrophysiologic techniques eventually help in this regard and in decision-making remains to be determined. In the meantime, cultural, religious, and family values will govern the responses of relatives to a patient in a minimally conscious state, and health-care providers must respect these responses and the previously expressed wishes of patients.

In the context of both the persistent vegetative and minimally conscious states, clinicians must be careful about suggesting at an early stage that no hope exists of useful recovery in order to justify decisions to discontinue life-supporting therapy when the evidence is lacking. Instead, a frank discussion of the limited information available and the generally poor (but uncertain) prognosis may be ethically more appropriate and lead to more informed management decisions.

The serial clinical assessment of patients in both the acute and chronic setting will help to detect subtle but important changes that may otherwise pass unnoticed and that may affect management. It will also help to clarify for family members the significance of any changes that they have themselves observed. For example, relatives and friends may assume that eye opening, eye movements, swallowing movements, smiling, and other motor activities represent signs of recovery when they develop in a comatose subject, and it is incumbent on physicians to explain that this is not the case so that realistic expectations can be maintained.

Functional imaging may also come to be important in the assessment of these patients. In minimally conscious patients, activation patterns similar to those of healthy subjects have been described and suggest conscious awareness. In patients diagnosed as being in a vegetative state, changes in positron emission tomography or functional magnetic resonance imaging sometimes reveal cortical activation, for example, in response to face-recognition or speech-perception paradigms, instructions to imagine motor activity, or a familiar voice saying the patient's name. Such findings suggest awareness similar to that in patients in a minimally conscious state and may help to indicate which patients behaviorally classified as in a vegetative state are in fact in a minimally conscious state or are likely to recover clinical signs of awareness, thereby providing a guide to prognosis.

There have been occasional anecdotal cases in the lay media of apparently miraculous recovery from a prolonged vegetative or minimally conscious state. The accuracy of some of these reports is unclear, as is the extent to which any recovery was clinically meaningful. Reports of arousal after deep brain stimulation of minimally conscious patients are intriguing. Chudy and associates have reported that with stimulation of the centromedian-parafascicular complex, two of four patients in a minimally conscious state regained consciousness and the ability to walk, speak fluently, and live independently, and a third patient recover consciousness, but remained chairbound.[12]

There are anecdotal reports of arousal and temporary improvement after administration of zolpidem to patients in a persistent vegetative or minimally conscious state. Noormandi and co-workers reviewed specifically the effects of zolpidem on disorders of consciousness, finding that it provided temporary benefit in some but not all patients, and specifically those with nonbrainstem injuries. Patients with post-anoxic encephalopathy or traumatic brain injury were not helped.[13] There are also reports of patients with disorders of consciousness responding to amantadine or apomorphine,[14] but the findings are conflicting and not well substantiated. It appears that in a few patients with abnormalities of arousal or responsiveness, certain interventions may lead to temporary improvement. The systematic evaluation of function in brain-injured patients and of the effects of various manipulations on arousal and prognostication may be rewarding. In the meantime, it is the responsibility of medical and paramedical staff to ensure that anecdotal case reports are not taken out of context and do not result in unrealistic expectations by family and friends attempting to come to terms with the predicament of a patient in a vegetative or minimally conscious state.

De-efferented State

Patients in a "locked-in" or de-efferented state are conscious but quadriplegic and incapable of communication except by eye closure or vertical eye movements. They typically are ventilator dependent. They may be excluded erroneously from clinical decision-making unless the impediment to normal communication is recognized and steps are taken to facilitate other means of communication.

Depending on its cause, locked-in patients may survive for many years and some may even regain some motor functions, such as some recovery of head movement. Nevertheless, the probability of regaining physical autonomy in daily life is remote. Despite their severe motor disability, many of these patients feel that their quality of life is good and certainly better than it is rated by their primary caregiver or spouse. Psychologic adjustment to their disease and its limitations relates to problem-oriented coping strategies, such as developing a communication code, and to perceived social support.[15] Thus, the widely held view that patients with severe disability inevitably have a poor quality of life, become despondent, and come to wish for death is not necessarily true. The quality of life may be acceptable to patients despite severe handicap, and although suicidal thought may occasionally surface there are typically few requests for euthanasia among such patients. Indeed, they almost always indicate their preference to be resuscitated if necessary,[15] an important consideration for those responsible for their care and interacting with affected families.

Nevertheless, some de-efferented patients may decide on withdrawal from further life support, and clinicians are obligated to respect these decisions when they have been made competently. The withdrawal of support must be accompanied by measures to minimize further pain and distress while the patient succumbs.

Advanced Dementia

Meta-analyses indicate that from 60 years of age, the prevalence of dementia doubles with every 5 years of age. Unfortunately, however, only a minority of patients with dementia or their surrogates engage in advance planning for end-of-life care or benefit from palliative care or hospice services. Patients in the early stages of progressive dementing disorders should be encouraged to make their preferences known by discussion with family and healthcare providers and by written advance directives while they are still competent. They often are reluctant to plan ahead, however, either because of a failure to accept that a fatal outcome is likely, because they find such discussions distasteful, or because they prefer to leave such decisions to others. In the absence of such written directives, a proxy decision-maker will need to act for the patient. Well-staffed comprehensive care programs for patients with dementia improve end-of-life care and planning for the future, but financial support for such programs is generally limited.

The management of patients with advanced dementia may be especially challenging for neurologists. Cognitive decline and the disintegration of personality do not justify any disregard of and loss of respect for the individual patient. Medical problems require as much attention as in patients who are cognitively intact. This is particularly difficult because demented patients are often unable to cooperate fully, making the recognition and management of such problems more demanding. The care of patients with advanced dementia requires close interaction of clinicians with other family members to improve the quality of life and to find practical solutions for the minor problems that complicate daily life. Depression may enhance an apparent cognitive decline and may even be mistaken for dementia; the possibility of its presence always merits consideration.

The long-term prognosis of patients with dementia depends in part on the type or cause of the cognitive failure and this—in turn—may affect patient survival, caregiver burden, need for institutionalization, and planning for patient needs. Patients with advanced dementia are not necessarily terminally ill but they may undergo a protracted period during which they are unable to speak or respond to their environment. Decisions about life-sustaining treatment for them are then usually made by reference to the same ethical and legal principles as for dying patients, although there is no unanimity in this regard. In such circumstances, for example, the artificial provision of nutrition and hydration in a demented patient who has lost the ability to eat is best decided based on the previously expressed wishes of the patient or the decision of a surrogate.[7] Palliative care is the preferred approach and is often provided in a nursing-home or hospice environment, although not always satisfactorily.[16]

In one study of patients with advanced dementia living in nursing homes, almost 55 percent died over an 18-month period; the probability of death within 6 months was approximately 25 percent.[16] Among those who died, pneumonia occurred in 37 percent, febrile episodes in 32 percent, and eating problems in 90 percent in the last 3 months of life. Distressing symptoms were common—dyspnea or pain for at least 5 days per month occurred in 46 and 39 percent, respectively; pressure ulcers in 39 percent; agitation in 54 percent; and aspiration in 41 percent. Such symptoms became more common as the end of life approached. Many patients underwent burdensome interventions of uncertain benefit, such as tube-feeding or parenteral therapy, or hospitalization, within 3 months of death.[16] In many instances, such interventions were not necessitated by the need to reduce physical suffering and were inconsistent with a palliative approach to care. Studies show that despite traditional medical and nursing care, many demented patients—who are unable to communicate their physical or emotional needs—experience increasing amounts of suffering as death approaches.

Ambiguity about the care of severely demented patients and their families is common. Thus, Wray and co-workers found a major difference between the decision to limit care, which usually involved the patient's family, and the decision to provide full care, which involved families less often.[17] The physicians involved in these decisions often thought that less intensive care would have been more appropriate, but nevertheless provided full care because the acute condition was potentially reversible (e.g., with antibiotics). Morrison and Siu compared the care received by patients admitted to a New York hospital for hip fracture or pneumonia and who had either advanced dementia or intact cognition.[18] The demented patients received as many burdensome procedures as the nondemented patients. Moreover, in the group with hip fracture, patients with dementia received significantly fewer morphine sulfate equivalents daily for pain relief than patients with preserved cognition, and only 24 percent received a standing order for any analgesics, even though such patients are often unable to communicate the presence of pain. Even fewer of the demented than nondemented patients had advance directives, and no documentation was found of any discussion about goals of care or decisions to withhold life-sustaining therapies in 90 percent of the patients with severe dementia.

A major problem in the management of severely demented patients is to recognize when they are actually dying. Indicators that they are approaching the end of life may be subtle physical or behavioral changes, such as nonverbal signs of pain or discomfort, that are not easily recognized by inexperienced staff unfamiliar with the patient. Whenever possible, patients should be allowed to die in familiar surroundings, such as a nursing home rather than in an acute care facility.

The benefits of tube feeding patients with advanced dementia who have difficulty in eating have been questioned. There is little or no evidence that malnutrition is prevented or that tube feeding is associated with greater comfort, improved functional status, or longer survival. To the contrary, placement of a tube may increase patient discomfort or suffering, and tube feeding may be associated with adverse effects such as the increased use of restraints. In many circumstances, hand feeding may be preferred despite the involved cost because it is more comfortable for patients.

The understanding, knowledge, and perceptions of healthcare proxies of nursing-home residents with advanced dementia influence the care that patients receive. Because the ability of patients with dementia to communicate declines with time until grossly impaired, proxies and healthcare professionals must interpret patient behavior with particular care. When proxies are well informed and have a realistic understanding of the clinical complications expected in advanced dementia, patients are less likely to undergo unnecessary aggressive interventions in the final 3 months of life. Clearly, close consultation with family members and surrogates is necessary to define a rational treatment and management approach, which can then be followed. Bereaved family members may—in turn—require continuing support by someone on the healthcare team after the patient's death.

Amyotrophic Lateral Sclerosis

For this incurable disease, early palliative care is important and is directed at maximizing quality of life as soon as the diagnosis is made. Hospice care in the terminal stages of the disease may help in the control of symptoms and with ensuring a peaceful death.

Ganzini and co-workers measured pain, quality of life, suffering, sense of hopelessness, depression, level of disability, desire for life-sustaining medical treatment, and interest in assisted suicide of patients with amyotrophic lateral sclerosis and also asked their caregivers to rate the patients' quality of life, pain, and suffering.[19] Suffering was graded as 4 or more on a 6-point scale by 20 percent of patients and correlated with increasing pain, hopelessness, and level of disability. No relationship was found, however, between ratings of pain, suffering, and quality of life and interest in life-sustaining treatment or physician-assisted suicide. Pain and depression were often unrecognized or inadequately managed by treating physicians.

Nevertheless, most patients in the dying phase of amyotrophic lateral sclerosis die peacefully and, despite the common fear of suffocation, patients rarely choke to death. The most frequent symptoms in the last 24 hours are dyspnea, coughing, anxiety, fear, and restlessness. About half the patients die at home. The main palliative measures in use include ventilatory support, percutaneous gastrostomy, morphine, and benzodiazepines.

Regardless, early involvement of multidisciplinary palliative care services (such as neurologists and other specialty physicians; nursing staff; physical, occupational, and respiratory therapists; speech pathologist; dietician; medical social worker; and pastoral counselor) in the management of patients and their families, that is, before the terminal phase of illness, would probably improve the quality of life over the course of the disease and help to ensure integrated care by physicians and paramedical personnel.

In patients with amyotrophic lateral sclerosis, ventilatory support should be discussed before the development of respiratory symptoms, and noninvasive ventilation should be considered before tracheostomy. Noninvasive positive-pressure ventilation may postpone the need for tracheostomy and mechanical ventilation, and may improve hypoventilatory symptoms, cognitive function, and quality of life. The financial, social, and emotional burden of chronic invasive ventilation must be discussed fully with patients and their families so that informed decisions can be made.

As the disease progresses, the goal of treatment evolves from optimizing and maximizing function to palliative care. Two of the most common distressing symptoms in advanced cases are dyspnea and mood disorders or anxiety, which must be treated appropriately. Pain may also occur and, if non-narcotic analgesics, anti-inflammatory drugs, and antispasticity agents are inadequate, may necessitate opioids. Sialorrhea can be managed by positioning and suction, by pharmacologic means, or with botulinum toxin injected into the parotid and submandibular glands. Low-dose radiation has also been used successfully in this context. Sleep disturbances are frequent and may be helped by treating mood disorders, respiratory inadequacy, bulbar dysfunction (by managing sialorrhea that is leading to choking episodes), and the inability to turn in bed (frequent repositioning; use of a hospital bed and mattress).

The wishes of patients with amyotrophic lateral sclerosis concerning life-sustaining therapy are not stable, and preferences frequently change over time. Frequent discussion of options is therefore important, and advance directives for end-of-life care require periodic re-evaluation. Discussions should not be delayed until there is a crisis. Issues to be discussed include the maintenance of nutrition; the desired extent of respiratory support, including the use of noninvasive and invasive ventilation; and measures to combat infection. Such discussions are never easy or straightforward, and many physicians lack any training in these areas. It is important to accept the autonomy of patients in end-of-life decisions and their right to request or refuse interventions to sustain life. The situation may be complicated by concerns about decision-making capacity due to the cognitive impairment that occurs in many patients with amyotrophic lateral sclerosis, some of whom will develop frank frontotemporal dementia. This makes it important that surrogate decision-makers are appointed early, especially if there is evidence that cognition is becoming impaired.

Patients and caregivers will not agree on all issues. Patients tend to overestimate the quality of life of their caregivers, whereas caregivers underestimate that of patients. Both patients and caregivers may endorse the future use of noninvasive mechanical ventilation, but patients are often more uncertain than caregivers. There is usually little interest in invasive ventilation. Spirituality or religion influences the readiness to accept percutaneous endoscopic gastrostomy, noninvasive or invasive assisted ventilation, and attitude toward the process of dying. Thus, psychosocial factors, personality traits, and spiritual factors, in addition to symptoms and disability, require consideration and discussion with patients and families throughout the illness.

The incidence and predictors of percutaneous endoscopic gastrostomy have been examined in a group of patients with amyotrophic lateral sclerosis.[20] Patients undergoing percutaneous endoscopic gastrostomy were more likely than otherwise to undergo tracheostomy, more likely to have had a baseline preference for the procedure, and more likely to have initiated healthcare proxies early in the disease course. The results imply that use of percutaneous endoscopic gastrostomy is part of a consistently proactive approach to the disease among patients and their supporting family. Gastrostomy may improve patients' quality of life but there is little evidence that it improves survival.

These various interventions to support nutrition and ventilation are often determined by clinical need, but their application depends on choices made by patients and surrogates, which—in turn—are influenced by such factors as cognitive and affective status, personality, educational background, cultural factors, income, and differences in healthcare systems. In some instances, interventions—which do not arrest disease progression—necessitate institutionalization and a reduced quality of life.

CONCLUDING COMMENTS

Physical distress remains common in many patients facing the end of life, but fear of suffering is probably even more common. Greater education of healthcare providers about palliative medicine and easier access for patients to hospice programs and related esources will help to improve care for those who are dying. The apprehensions of dying patients may also be diminished by the knowledge that caregivers are fully committed to prevent, limit, or treat any discomfort that might arise. It is not possible to guarantee an "easy" death, but a commitment to provide optimal care is certainly realistic and reassuring. Such care must take into account the wishes of patients and their families.

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Index

Note: Page numbers followed by "*f*" and "*t*" refer to figures and tables, respectively.

A

ABCD1 gene, 1073
Abdominal aorta, 27, 36–37. *See also* Aorta; Aortic aneurysms; Aortic arch; Aortic disease; Aortic surgery; Aortitis
  anatomy of, 31*f*
  atherosclerotic disease of, 961
Abdominal aortic aneurysms
  neurologic function disturbances associated with, 28, 35*t*, 37
  rupture of, 37
Abducens nerve palsy, 310–311, 354, 422, 427, 429, 693, 700, 871–872, 985
Aβ40 protein, 987
Abetalipoproteinemia, 208–209, 242, 446–447
Abscess, 790, 793
  brain. *See* Brain abscess
  cerebellar, 693
  epidural. *See* Epidural abscess
  infective endocarditis, brain abscess and, 59–60, 76–77
  temporal lobe, 693
  Toxoplasma, 1030
Abscopal phenomenon, 481
Absolute stroke risk reduction (ARR), 78
Acanthamoeba spp., 822*t*, 830–831
Acanthocytes/acanthocytosis, 208–209, 322, 446–447, 1024
Acetaminophen, 1052
  hypothermia and, 667*t*
  during lactation, 582
  for migraine, 581–582
Acetazolamide, 18, 321, 423, 583, 614, 624, 817, 953, 1038–1039
Acetylcholine, 139–140, 140*f*, 158, 218, 318*f*, 324–325, 435, 518, 542–543, 543*f*, 554–555, 560, 657, 914, 987, 1075, 1090
Acetylcholine receptor (AChR) antibodies, 14, 129, 230–231, 295, 426*t*, 429–430, 505, 518–519, 547, 597, 620, 973, 1015*t*, 1076
Acetylcholinesterase, 225, 324–325, 656
Acetylcholinesterase inhibitors, 324–325, 430, 518–519, 607, 656, 969, 1100
Achlorhydria, 237
Acid maltase deficiency, 15–16, 997*t*
Acoustic neuroma, 324, 345, 401, 404*f*, 408
Acquired cardiac disease, neurologic manifestations of, 65–84
Acquired central hypoventilation, 9
Acquired hemophilia A, 462
Acrodermatitis enteropathica, 362*t*
Acromegaly, 306*t*, 331, 333, 334*t*, 340, 500*t*, 925, 1064–1065, 1064*t*, 1068, 1077, 1077*t*
Acrylamide neuropathy, 129, 649, 1064*t*
Actigraphy, 916–918, 927, 929*f*
Action myoclonus, 1035
Activated protein C (APC), 177
Active core rewarming, for hypothermia, 670
Active external rewarming, for hypothermia, 670
Acute abdomen, 228
Acute bacterial meningitis. *See* Bacterial meningitis
Acute disseminated encephalomyelitis (ADEM), 761, 762*f*, 855, 858
Acute inflammatory demyelinating polyneuropathy. *See* Guillain–Barré syndrome
Acute inflammatory demyelinating polyradiculoneuropathy, 46, 1069
Acute intermittent porphyria (AIP), 230, 325, 336, 336*t*, 1016–1017, 1073. *See also* Guillain–Barré syndrome
Acute motor axonal neuropathy, 1069
Acute motor–sensory axonal neuropathy (AMSAN), 1069–1070
Acute myelomonocytic leukemia, 447–448
Acute myocardial infarction, 66–67, 66*t*, 69, 74, 80, 158–159, 161, 164, 166
Acute pandysautonomia, 128–129, 1069–1070
Acute peripheral neuropathy, 228, 1069–1070
Acute promyelocytic leukemia, 182
Acute quadriplegic myopathy, 623–624
Acute symptomatic seizures, 1007–1008
  in children with congenital heart disease, 60–61
Acute tubular necrosis, myoglobinuria and, 1083–1084
Acyclovir, 605*t*, 606–608, 612*t*, 743*t*, 748, 751*t*
  and bacterial meningitis, 688*t*
  for herpes simplex virus encephalitis, 743*t*, 750–751
  for herpes simplex virus meningitis, 688, 743*t*, 746, 748, 751*t*
  pharmacokinetics of, 750–751
  for varicella zoster infection, 752, 1060–1061
  for viral encephalitis, 757, 759
Adams–Oliver aplasia cutis congenita type III, 352*t*
ADAMTS13, 357–358
Addison disease
  cerebral symptoms of, 278
  description of, 339
  effective blood volume reductions from, 125
Adenomas
  adrenal, 339, 339*t*
  parathyroid, 279, 337
  pituitary, 324, 328–333, 334*t*, 336–337, 421, 421*t*, 429, 567–568, 582, 586
Adenosine, 161, 168, 914, 1014*t*, 1021
Adenosine triphosphate (ATP), 148, 242, 661, 1025, 1074, 1089
Adhesive arachnoiditis, 983*t*
Adie tonic pupil, 434, 436

Adjuvants and preservatives, 856–857
Adolescents, sleep requirements in, 914
Adrenal cortex
  cells of, 338
  Cushing syndrome, 338–339
  disorders of, 338–339
  primary aldosteronism, 338
  secretions by, 338
Adrenal glands, 338–339. *See also* Adrenal cortex; Adrenal medulla
Adrenal insufficiency, 339
  acute, 333
  causes of, 339*t*
  primary, 339
  secondary, 339
Adrenal medulla
  chromaffin cells of, 338
  neuroendocrine tumors, 340, 1060
  pheochromocytoma, 340
Adrenocorticotropic hormone (ACTH), 158, 332
Adrenomyeloneuropathy, 339, 1073
Advanced glycation end-product (AGE) pathway, 314
Advanced sleep phase disorder, 928–929, 929*f*
Aerobic exercise, 678
  and neuroplasticity, 678
African trypanosomiasis, 828–829, 828*f*
Agalsidase alfa, 267
Agalsidase beta, 267
Aging
  frontotemporal dementia and, 1101–1102
  HIV and, 773
  neuro-otologic manifestations of, 412–413
  postural hypotension associated with, 125–126
  sexual function affected by, 562–563
  sleep apnea and, 924
Agitation, 60, 1106–1108
AIDS. *See also* Human immunodeficiency virus
  in children, 589
  cryptococcal meningitis in, 814–815
  dementia complex, 1103
  maternal, children born to women with, 590
  neurocutaneous manifestations of, 352*t*, 359, 366*t*
  progressive multifocal leukoencephalopathy (PML) in, 757–758, 775–777, 780
  toxoplasmosis in, 825–826, 826*f*
Airways, mechanical inputs from, 4–5
Akathisia, 609, 642, 1027
Alagille syndrome, 58
Albendazole, 833, 847
  for cystic echinococcosis, 833
  for cysticercosis, 833
  for neurotrichinosis, 834
Alberta Stroke Program Early CT score (ASPECTS), 67–68
Alcohol
  hyperthermia and, 666*t*
  hypothermia and, 667*t*
  intoxication caused by, 627
  postoperative delirium, 981
  and stroke, 184, 184*f*, 635
Alcohol withdrawal, 627–629
  description of, 627
  delirium tremens after, 628–629
  seizures caused by, 628, 1020
Alcoholism
  neurocutaneous manifestations of, 357*t*, 366*t*
  postural hypotension associated with, 128
  stroke risks associated with, 184, 184*f*
  thiamine deficiency secondary to, 630
Alcohol-related disorders, 628*f*
  central pontine myelinolysis, 633
  cerebellar degeneration, 632–633
  dementia, 629
  hepatocerebral disorders, 632
  Korsakoff syndrome, 630–631
  Marchiafava–Bignami disease, 631–632
  myopathy, 634–635, 1082
  neuropathy, 634–635, 1072
  pellagra, 631
  stroke, 635
  Wernicke encephalopathy, 209, 244, 245*f*, 629–630
Aldose reductase inhibitors, 308, 1068
Aldosterone, 142, 278, 338
Alectinib, 492
Alemtuzumab, 463
  during pregnancy, 594
Alendronate, for hemifacial spasm, 386
Alexander law, 432
Alkylating agents, 526
  ifosfamide, 526
  temozolomide, 482*t*, 492, 522*t*, 523*t*, 526
Allogeneic transplantation
  hematopoietic cell, for osteopetrosis, 382–383
Allopregnanolone, 325–327
Almotriptan, 1050, 1052
α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) peptide, 674–675
α_1-antitrypsin deficiency, 105
Alpha blockers, 553–554
α-dystroglycan, 729
α-galactosidase A, 267
α-methyldopa, 608
Alpha-tocopherol transfer protein, 242
α-synuclein (Lewy neurites), 226, 1109
α-tocopherol transport protein (α-TTP) deficiency, 242
Alphaviruses, 741–742, 755
Alport syndrome, 270, 408
Alternate cover test, 424
Aluminum in childhood vaccines, 857
Aluminum salts, 857
Alveolar hypoventilation, 15, 17
Alzheimer disease
  agitation in, 1107
  anesthesia in, 987
  characteristics of, 324–325
  clinical features of, 312
  dementia caused by, 1099–1100
  diabetes mellitus and, 312
  estrogen and, 324–325
  gut dysmotility and, 225
  insulin resistance and, 314
  irregular sleep-wake disorder in, 936
  and neurosteroidogenesis, 325
  risk factors for, 1100
  seizures and, 969
  sex hormones and, 325–326
  sleep disorders in, 936
  sundowning in, 936
  systemic complications of, 1105*t*
  therapeutic vaccination for, 864
  treatment of, 225
Amantadine, 572*t*, 592, 608–611, 613, 668, 924, 966, 1026, 1033, 1035, 1036*t*, 1039, 1041, 1045, 1048*t*, 1118

AmBisome, 816
Ambroxol, 468
Amebiasis, cerebral, 831
Amenorrhea, hypothalamopituitary disorders and, 567
Amenorrhea-galactorrhea, 330–331
American trypanosomiasis, 74
Aminoglycoside antibiotics
  neuromuscular transmission disorder and, 619–620
  ototoxicity caused by, 410, 410*f*
  ventilatory depression secondary to, 619
Amiodarone, 129, 168, 293, 416*t*, 604, 611, 612*t*, 614–615, 618, 624, 1012, 1039*t*, 1064*t*
Amitriptyline, during pregnancy, 582
Amlodipine, 1008, 1049
Amnesia, 244, 470, 525, 576, 627, 630, 641, 674, 749*t*, 751, 779, 792, 919, 924, 934, 1022
Amniotic fluid embolism, 584
Amotivational syndrome, 645
Amoxicillin, for Lyme disease, 714*t*
Amphetamines, 1020
  dyskinesias and, 1028
  hyperthermia and, 666*t*
  and stroke, 184–185
Amphotericin B, 816
  for coccidioidal meningitis, 817–818
  for cryptococcal meningitis, 814–816
Ampicillin, for bacterial meningitis, 688*t*
Amygdala, 126, 159, 166, 558, 561, 633, 944–945
Amyloid fibrils, 261
Amyloid neuropathy
  description of, 229–230
  lower urinary tract symptoms in, 547
Amyloidosis, 314
  β_2-microglobulin, 261
  neurocutaneous manifestations of, 352*t*, 366*t*
  polyneuropathy caused by, 1071
  primary, 1071
Amyotrophic lateral sclerosis (ALS), 13, 27, 226, 327, 354, 378*t*, 380, 384, 386, 501*t*, 514, 571, 652, 659, 679, 783, 856*t*, 972, 988, 1120–1121
  anesthesia in, 972, 988
  caregivers of, 1121
  dying phase of, 1121
  end of life care for, 1121–1122
  gut dysmotility and, 226
  life-sustaining therapy for, 1121
  noninvasive positive-pressure ventilation for, 1121
  palliative care for, 1120–1121
  pathogenesis of, 1058
  percutaneous endoscopic gastrostomy, 1121
  pulmonary function tests in, 13
  respiratory failure associated with, 13
  spinal anesthesia and, 972
  suffering in, 1120–1121
  ventilatory support for, 1121
Anabolic androgenic steroids and stroke, 183–184
Anaplastic lymphoma kinase (ALK) inhibitors, 492
Anemia
  in cold agglutinin disease, 445–446
  in cryoglobulinemia, 446
  folate deficiency, 444
  in hereditary spherocytosis, 445
  iron-deficiency, 442
  in kernicterus, 446
  neurologic manifestations of, 442–446
  in paroxysmal nocturnal hemoglobinuria, 445
  in sickle cell. *See* Sickle cell anemia
  in thalassemia, 445
  in tuberculous meningitis, 720
  in vitamin B_{12} deficiency. *See* Vitamin B_{12} deficiency
Anesthesia
  in Alzheimer disease, 987
  in amyotrophic lateral sclerosis, 988
  cognitive changes development after exposure to, 982
  coma after, 979–981
  consciousness impairment after, 979, 981*t*
  delayed awakening after, 979–981
  delirium and, 968
  in dysautonomia patients, 145
  in epilepsy, 988
  eustachian tube obstruction after, 984
  and headache, 986
  in Huntington disease, 988
  in intensive care unit, 988
  malignant hyperthermia and, 985
  in multiple sclerosis, 967
  in multiple system atrophy, 988
  neuraxial, 967
  in neurocritical care unit, 988–989
  neurologic complications of, 980*t*
  in neuromuscular disorders, 988
  in Parkinson disease, 987
  perioperative mental status changes, 979–981
  postoperative cognitive dysfunction after exposure to, 981–982
  regional, 966
    antithrombotics and, 983
    warfarin and, 983
  seizures after, 985
  spinal, 960–961
Aneurysm clips, and magnetic resonance imaging, 954
Aneurysm(s)
  aortic. *See* Abdominal aortic aneurysms; Aortic aneurysms
  atrial septal, 73
  cerebral. *See* Cerebral aneurysms
  endovascular, 961
  neoplastic, 182
Angel dust. *See* Phencyclidine
Angioedema, 366*t*
Angiography
  aortic, 959–960
  cerebral
    carotid artery puncture in, 960
    neurologic complications of, 959–960
    stroke risks, 959–960
    of vasculitis, 895
  diagnostic uses of, 106, 959
  intracranial aneurysm rupture during, 960
  neurologic complications of, 959
  peripheral, 961
  spinal, 960–961
Angiomatosis, 362*t*, 497
Angiostrongylus cantonensis, 822*t*, 834–835
Angiotensin II, 103, 119–121, 142–143, 338
Angiotensin II receptor blockers (ARBs), 103
Angiotensin receptor blocker, 259
Angiotensin-converting enzyme (ACE) inhibitors, 103, 868, 877, 1049–1050
  combination therapy with thiazide diuretic, 104–105
  for hypertension, 103
Angle-closure glaucoma, 436, 614
Anhidrosis, 127, 129, 139*f*, 312, 366*t*, 435–436, 547, 662–663, 731, 892

Anisocoria, 132, 428, 434–436, 985
  greater in light with abnormal pupillary light reaction, 435–436
  Horner syndrome and, 435
  physiologic, 434
  transient, 434
Ankylosing spondylitis, 36*t*, 351, 389–392, 390*f*
ANNA-1 antibodies, 129, 229, 502, 503*t*, 1015*t*, 1031, 1059–1060, 1071
Annexin V, 469
Anorectal manometry, 228
Anorgasmia, 559, 561, 568–569, 572*t*, 574
Anosmia, 362*t*, 534, 615, 676*t*, 677*t*, 761, 871, 1074
Anterior horn cell disorders, 12*t*, 13, 17*t*, 27, 247–248, 447, 552, 663, 863, 1000, 1058, 1060–1061
  acute poliomyelitis, 12*t*, 13, 17*t*, 589, 743*t*, 856*t*, 863, 1058–1059
  amyotrophic lateral sclerosis. *See* Amyotrophic lateral sclerosis
  respiratory insufficiency, 13
  types of, 1058–1059
Anterior inferior cerebellar artery, 404–405
Anterior ischemic optic neuropathy, 44–45
Anterior segment optical coherence tomography (AS-OCT), 213
Anterior spinal artery
  anatomy of, 22–23, 23*f*, 24*f*, 27
  branches of, 24*f*
  in cervical region, 23
  in lumbar region, 23
  in midthoracic region, 23
  peripheral arteries from, 24
  sulcal arteries from, 24, 24*f*
Anterior spinal artery syndrome, 27
Antiannexin A5, 176
Antiarrhythmic/antipsychotic drugs, 167
Anti-β2 glycoprotein-I antibodies (aβ2GPI), 176
Antibiotics, 694. *See also* Antimicrobial therapy
  ischemic stroke treated with, 95
  ototoxic, 613–614
  seizures and, 1021
  for vertebral osteomyelitis, 387–388
Anticardiolipin antibodies, 176, 393, 408, 470, 704
  systemic lupus erythematosus and, 887
Anti-CCP autoantibodies, 894
Anticholinergic agent, 145, 221, 225–226, 228, 436, 548*t*, 554, 572*t*, 605, 608, 611–612, 614, 616, 620, 665, 666*t*, 935–936, 968*t*, 969, 1024–1026, 1027*t*, 1028, 1032, 1038, 1041, 1045, 1106
  hyperthermia and, 666*t*
Anticholinesterase drugs, 14, 324–325, 506, 598, 656, 666*t*, 1075–1076, 1100
Anticitrullinated protein antibodies (anti-CCP), 894
Anticoagulant therapy, 47–48, 58–59, 72, 79, 173. *See also specific disorders*
  apixaban, 468
  in aseptic venous sinus thrombosis, 700
  for atrial fibrillation, 78–79
  bleeding and, 468
  in infective endocarditis, 96
    native valve endocarditis, 96
    prosthetic valve endocarditis, 96
  life-long, 50
  in patients with mechanical valve, 96–97
  perioperative stroke and, 975–976
  postoperative, 975
  in pregnancy, 584
  and risk of stroke recurrence in SLE, 181
  rivaroxaban, 79, 468
  with warfarin, 173
Anticonvulsants. *See Antiepileptic drugs and specific disorders*
Antidepressants, 221, 311, 315, 336, 336*t*, 402–404, 463, 492, 495, 572*t*, 575, 595–596, 606, 608–611, 612*t*, 614–616, 634, 664–665, 934, 985, 1035, 1083*t*
  insomnia and, 917*t*, 920
  mania caused by, 608
  movement disorders and, 608–611, 1026, 1029*t*, 1032, 1035, 1036*t*, 1038, 1039*t*
  for neuropathic pain, 495, 595–596, 752
  neuropathy caused by, 1064*t*
  seizures caused by, 606, 612*t*, 1020–1021
  serotonin syndrome and, 1035
  temperature changes caused by, 665, 667*t*
Antidiuretic hormone, 335–336
Antiepileptic (anticonvulsant) drugs, 45, 61, 787, 1008, 1011–1012, 1052. *See also specific disorders*
  albumin binding of, 1008
  in anoxic-ischemic encephalopathy, 1014–1015
  for brain abscess, 695
  cardiac disease and, 1012
  cognitive function affected by, 608–609
  in critically ill patients, 1012–1014
  dabigatran, 79
  dose adjustments for, 1010*t*
  drug interactions, 971
  early-onset seizures and, 1022
  epilepsy management using, 579
  fetal malformations and, 579
  hepatic cytochrome P450 microsomal enzyme system and, 320–321
  hepatocellular injury and, 1011
  hormonal changes caused by, 566
  hypersensitivity reactions, 1011
  for insomnia, 920
  for myoclonus, 1038
  oral contraceptive failure and, 321, 581
  pharmacokinetics of, 1010*t*
  in porphyria, 1016–1017
  during pregnancy, 580–581
  preoperative considerations, 970–971
  in renal disease, 1008–1009
  for seizures from brain metastases, 479
  for seizures in cysticercosis, 833
  for seizures in Hashimoto encephalopathy, 1016
  sodium channels affected by, 1012
  spermatozoa affected by, 566
  teratogenic effects of, 579–580, 591
  in transplantation patients, 786–787, 1017–1018
  tremor and, 1039*t*
  uremic convulsions and, 255
  withdrawal symptoms of, 580
Antigenic drift, 862
Antigenic shift, 862
Antigen(s)
  group, 1, 505
  group, 2, 505–506
  intracellular, 505
Antigliadin antibodies, 203–204
Antihistamines, hyperthermia and, 666*t*
Anti-Hu antibodies, 129, 229, 306*t*, 502*t*, 516, 892, 902, 1031, 1037, 1041, 1059, 1063*t*, 1071
Anti-La antibodies, 887, 891
Anti-LGl1 syndrome, 274, 506*t*, 1015
Antilymphoblast globulin, 793

Anti−MAG-associated peripheral neuropathy, 506*t*
Antimetabolites
  cytarabine, 524
  fludarabine, 121, 506*t*, 522*t*, 523, 523*t*, 606, 1070
  gemcitabine, 525
  methotrexate, 524−525
  nelarabine, 525
  neurologic complications of, 522*t*, 523−525
Antimicrobial therapy, 616, 618. *See also individual diseases*
  for bacterial meningitis, 688, 688*t*
  for brain abscess, 695
  for infective endocarditis, 95
  for Lyme disease, 711, 713−714
  for meningococcal meningitis, 689−690, 689*t*
  peripheral neuropathy caused by, 618
  for pneumococcal meningitis, 688−689, 689*t*
Antimuscarinic medications
  description of, 543
  neurogenic bladder dysfunction treated with, 553
Antimycobacterial therapy, for tuberculous meningitis, 780−781
Antineoplastic drugs, 229, 306*t*, 336, 605, 608, 617−618, 621*t*
Antineuronal antibodies, 181, 453, 505, 758, 856*t*, 1028
Antineuronal nuclear antibody, 1, 129, 229, 306*t*, 502*t*, 516, 892, 902, 1031, 1037, 1041, 1059, 1063*t*, 1071
Antineuronal nuclear antibody, 2, 129
Antineuronal nuclear autoantibodies, 1037
Anti-NMDAR antibodies, 761, 763
Anti-NMDAR syndrome, 506*t*
Antinuclear antibodies (ANAs), 232, 469, 887, 1066
Antiparkinsonian medication, 965−966
  during pregnancy, 592
Antiphosphatidylethanolamine (aPE), 176
Antiphosphatidylserine (aPS), 176
Antiphosphatidylserine-prothrombin antibodies (aPS/PT), 176
Antiphospholipid antibodies (aPL), 92, 175−176, 180−181, 469−471. *See also* Anticardiolipin antibodies; *individual disorders*
  infective endocarditis and, 91*t*, 92
  ischemic stroke and, 180−181, 350−351, 352*t*, 470−471, 1030
  Libman−Sacks endocarditis and, 180−181
  in pregnancy, 584−586
  systemic lupus erythematosus and, 175−176, 887−889, 1030
  thrombosis associated with, 468−469
  types of, 469
Antiphospholipid antibody syndrome, 77, 176, 1052. *See also individual disorders*
  chorea and, 887, 1030, 1032
  clinical features of, 350−351, 469−471, 887, 890, 1015−1016
  diagnosis of, 469
  disseminated intravascular syndrome versus, 465
  epilepsy and, 470
  myoclonus and, 1030, 1034
  neurocutaneous manifestations of, 351, 352*t*
  nonbacterial endocarditis risks, 887
  parkinsonism and, 1044−1045
  patent foramen ovale and, 474
  primary, 1030
  and stroke, 175−176
  systemic lupus erythematosus and, 887, 890, 1030
Antiplatelet agents, 78−79, 168, 259, 267, 405, 533, 600, 975
Antiplatelet therapy in infective endocarditis, 95−96
Antipsychotics, 167, 330, 336*t*, 572*t*, 605, 605*t*, 609−612, 612*t*, 620*t*, 664, 666*t*, 920, 969, 1014*t*, 1021, 1026−1028, 1027*t*, 1036*t*, 1042, 1044−1045, 1105*t*, 1107−1108
  akathisia secondary to, 610
  atypical
    for insomnia, 920
    pregnancy and, 589
    tardive dyskinesia and, 1026
  dementia, uses of, 969, 1107
  neuroleptic malignant syndrome and, 612
  seizures and, 1021
Antirejection medications, 793, 1017, 1052−1053
Antiretroviral therapy (ART), 75, 359, 389, 589, 720, 736, 739, 747, 757, 767−774, 790, 805, 842, 1018, 1044, 1068, 1103
  CD8$^+$ T-cell encephalitis, 772
  central neurotoxicity of, 774
  CNS-penetration effectiveness of, 771*t*
  and cryptococcal meningitis, 816
  dideoxynucleoside, 1068
  leprosy and, 736
  life expectancy affected by, 773
  mechanism of action, 767
  progressive neurologic disease despite, 771−772
Antirheumatic drugs, 617*t*, 618, 620*t*, 621*t*, 897
Anti-Ro antibodies, 887, 891
Antiseizure medications (ASMs). *See* Antiepileptic (anticonvulsant) drugs
Anti-SRP antibodies, 1080
Antisulfatide antibody neuropathy, 452
Antisynthetase autoantibodies, 898
Antithrombin, 471
Antithrombin III deficiency
  pre-eclampsia and, 599
  stroke and, 176−177, 319−320, 471, 473, 583−586
Antithrombotics, 57
  perioperative stroke and, 975−976
  regional anesthesia and, 983
Antithymocyte globulins, 793
Anti-thyroglobulin antibodies, 300
Antithyroid antibodies, 300−301, 1016
Antituberculous drugs
  chemotherapy use of, 723−724
  folate deficiency and, 239, 239*t*
  seizure threshold and, 1014
  for tuberculous osteomyelitis, 389
Anti-Yo antibody, 505, 1071
Aorta, 21
  coarctation of, 38−39
    neurologic sequelae of, 38, 38*t*
    steal in, 39*f*
    subarachnoid hemorrhage associated with, 38
    surgical treatment of, 39−40
  Takayasu arteritis involvement of, 29, 36, 38, 904
  terminal, 32*f*, 33*f*
  thoracic
    aneurysms of, 37−38
    surgery of, 39−40
    traumatic rupture of, 38
  traumatic injury of, 38
Aortic aneurysms, 37−38
  abdominal
    neurologic function disturbances and, 28, 35*t*, 37
    rupture of, 37
  atherosclerosis as cause of, 37
  dissecting, 37−38, 37*t*
  distribution of, 37*t*
  neurologic function disturbances associated with, 37
  nondissecting, 37, 37*t*
  radiculopathies caused by, 32
  surgical treatment of, 39−40
Aortic angiography, 959−960

- Aortic arch
  - anatomy of, 28, 33*f*
  - atherosclerosis of, 29, 118
  - subclavian steal syndrome in, 30*f*
  - vascular anatomy of, 29*f*
- Aortic atheroma, 47
- Aortic disease
  - aneurysms. *See* Aortic aneurysms
  - aortitis. *See* Aortitis
  - coarctation of the aorta, 38–39, 38*t*, 39*f*
  - male sexual function affected by, 35, 35*t*
  - neurologic syndromes caused by, 21–35
    - autonomic neuropathies, 33–35
    - cerebral ischemia, 28–31, 29*f*, 30*f*
    - mononeuropathies, 31–32
    - peripheral neuropathy, 31–35
    - polyneuropathies, 32–33
    - radiculopathies, 32
    - spinal cord ischemia, 22–28
    - stroke, 28–31
    - transient ischemic attacks, 28–31
  - sexual function disorders secondary to, 34–35, 35*t*
- Aortic occlusion, distal, 26
- Aortic pathology, 21–35
  - cerebral ischemia, 28–31
    - anatomy, 28
    - strokes and transient ischemic attacks, 28–31
  - peripheral neuropathy, 31–35
    - autonomic neuropathies, 33–35
    - mononeuropathies, 31–32
    - polyneuropathies, 32–33
    - radiculopathies, 32
  - spinal cord ischemia, 22–28
    - anatomy, 22–24
    - ischemic cord syndromes, 24–28
- Aortic stenosis surgery, 50
- Aortic surgery, 39–40
  - aortography, 40
  - femoral nerve injury caused by, 31–32
  - male sexual function affected by, 35
  - motor evoked potentials during, 40
  - neurologic complications of, 39–40
  - somatosensory evoked potentials during, 40
  - spinal cord ischemia, intraoperative adjuncts to avoid, 40
  - spinal cord ischemia secondary to, 25–26, 26*f*, 26*t*, 39–40, 40*t*
- Aortic valve insufficiency, in Takayasu arteritis, 904
- Aortic valve replacement, 43
  - surgical, 49–50
- Aortic valve stenosis, 76
- Aortitis, 35–37
  - causes of, 36*t*
  - giant cell arteritis (GCA), 36–37
  - nonstenosing, 36*t*
  - stenosing, 36*t*
  - syphilitic, 36
  - Takayasu arteritis. *See* Takayasu arteritis (TAK)
- Aortography, 40
- Apixaban, 79, 259, 468, 983
- Apnea
  - obstructive sleep. *See* Obstructive sleep apnea (OSA)
  - posthyperventilation, 9
- Apnea-hypopnea index, 924
- Apneustic breathing, 8
- Apolipoprotein E, 314
- Apolipoprotein E ε2 allele, 54–55
- Apoptosis
  - after cardiac arrest, 148, 153, 158
  - ototoxicity and, 410
  - secondary cell death through, 994
  - sepsis and, 994–995
  - tumor cells and, 501, 525
- Apparent diffusion coefficient (ADC), 153, 478, 523–524
- Apraclonidine testing, 435
- Apraxia
  - of breathing, 9
  - corticobasal degeneration and, 1102
  - of eye opening, 1102
  - oculomotor, 467
  - of speech, 1102
  - of swallowing, 1105
- Aquaporin-4 (AQP4), 502, 514
- Aqueductal stenosis with hydrocephalus, 748
- Ara-C, 523*t*, 524
- Arachnoid cysts, 330*t*, 955
- Arachnoiditis, 390–391, 530, 531*t*, 717, 805, 808, 811, 818, 832, 875, 958, 984, 1059–1060
  - adhesive, 983*t*
  - tuberculous. *See* Tuberculous arachnoiditis, spinal
- Arginine vasopressin, 124, 130, 328, 335, 554
- Argyll Robertson pupils, 434, 706–707
- Armodafinil, 922–923, 922*t*, 927, 930
- Arnold–Chiari malformation
  - dysphagia and, 219, 227
  - erectile dysfunction and, 570
  - hypoventilation and, 17*t*
  - periodic alternating nystagmus and, 432
  - vestibular dysfunction and, 402–405, 432
- Arousal, 1085–1086
- Arousal disorders, 934
- Arousal stage, of sexual response
  - physiology of, 558–560, 563–564
  - tremor during, in Parkinson disease, 566–567
- Arrhythmia, cardiac, 66*t*, 69, 83, 158, 165–166, 311–312, 346, 458, 598, 629, 635, 638, 656–657, 657*t*, 671, 875, 920, 971, 979–980, 985, 1005, 1012, 1082–1084. *See also* Atrial fibrillation (AF); Atrial flutter
  - after acute stroke, 165
  - channelopathies, 83–84
  - conduction abnormalities, 83
  - in obstructive sleep apnea, 18
- Arsenic poisoning, 129, 366*t*, 614, 648, 1036*t*, 1039*t*, 1064*t*, 1065*t*, 1073, 1083
- Arsenicals, 614
- Arterial emboli, 65–66, 70, 87, 496
- Arteriovenous malformations (AVMs), 92*t*, 108, 173, 349, 377, 548*t*, 583, 586*f*, 587–588, 961, 1042
  - cerebral, in pregnancy, 583, 586–587, 586*f*
  - endovascular treatment of, 961
  - intramedullary, 962
  - spinal, in pregnancy, 587–588
- Arteritic ischemic optic neuropathy, giant-cell arteritis (GCA) and, 903
- Arteritic posterior ischemic optic neuropathy, 420*t*
- Arteritis
  - giant cell, 902–904
  - Takayasu. *See* Takayasu arteritis
  - temporal, 902
- Artery of Adamkiewicz, 22*f*, 23, 960–961
- Arthropod-borne viruses. *See also specific virus*
  - encephalitis caused by, 687, 749, 754–755
  - meningitis caused by, 746
- Articulation deficits of speech, 943

AS01B, adjuvant suspension, 857
Ascending arousal system, 914
Ascending paralysis, acute, 902
Aseptic meningitis. *See also* Viral meningitis
  cerebrospinal fluid pleocytosis and, 957–958
  chemotherapeutic agents and, 523*t*, 524–525, 529–530, 530*t*
  definition of, 748
  drug-induced, 604
  entervirus PCR assay and, 747
  epidural block and, 983*t*
  fungal disease and, 722
  human immunodeficiency virus and, 775
  intrathecal contrast administration, 957–958
  Kawasaki disease, 900
  Lyme borreliosis, 352*t*, 354
  mumps vaccination and, 860
  Mycoplasma pneumoniae infection, 1028–1030
  neurosarcoidosis and, 355, 869, 871*t*, 872–873, 881, 883
  from occult bacteria, 748
  poliovirus infection and, 1058
  prednisone for, 880
  relapsing polychondritis, 393–394
  in Sjogren disease, 352*t*
  spinal block and, 983*t*
  subarachnoid hemorrhage and, 88–91
  systemic lupus erythematosus and, 355, 888–889
  toxoplasmosis and, 748
  treatment of, 881
Aspergillus fumigatus, 179*t*, 267, 787, 843
  diagnostic testing, 843
  presentation, 843
  risk factors, 843
  treatment, 843–844
Aspergillus spp., 788, 790, 792, 804–805, 804*t*, 807, 810, 814, 818–819, 842
Aspiration
  in dementia, 1104–1106
  dietary modifications for, 1104–1106
  tube feeding and, 1105–1106
Aspirin, 50
  for giant cell arteritis, 904
  herpes zoster and, 752
  overuse, headache and, 1048
  platelet function and, 63
  for stroke risk reduction, 50, 76, 78–80, 114, 116, 180, 584, 599–600, 605, 614, 975
  for systemic lupus erythematosus, 889, 1030
  toxicity and, 614–615
Asterixis
  hepatic insufficiency and, 1034
  hyperammonemia and, 980
  in uremic encephalopathy, 252–253
Asthma and headache, 1051
Astrocytes, 995
  swelling of, in hepatic encephalopathy, 196–197
Astroglial tumors, 323
Asymptomatic neurocognitive impairment, 767–768, 768*t*
Asystole, 165–166
Ataxia, 208, 523*t*. *See also specific disorders*
  in abetalipoproteinemia, 208–209, 446–447
  alcoholic cerebellar degeneration and, 632
  celiac disease and, 203
  in Chiari malformation, 405, 405*f*
  in copper deficiency, 210, 240
  diabetic polyneuropathy and, 305, 313*f*
  in folate deficiency, 444
  of gait, 202, 631
  gluten, 203–204
  Hashimoto encephalopathy and, 300
  with hemangioblastoma, cerebellar, 456
  hepatic encephalopathy and, 191, 195*f*
  in hyperparathyroidism, 279
  in hyponatremia, 274
  in hypothyroidism, 286, 289
  iatrogenic, 524, 526–527, 532, 612, 616
  in Miller Fisher syndrome, 429
  neurocutaneous disorders and, 362–364, 362*t*
  ocular motor palsies, 429
  Paget disease of bone, 384
  in pancreatic encephalopathy, 200
  paraneoplastic, cerebellar, 506*t*, 509–512
  in uremic encephalopathy, 252, 255*f*
  viruses causing, 763*t*
  in vitamin B_{12} deficiency, 237
  in vitamin E deficiency, 208, 242
  in Wernicke encephalopathy, 209, 244, 245*f*, 411, 629–630. *See also* Alcohol
  in Wilson disease, 212
Ataxia-telangiectasia, 362*t*, 363
Ataxic breathing, 8, 10–11
Ataxic hemiparesis, 113
Atenolol, 1049, 1051
Atezolizumab, 529
Atherosclerosis, 29, 29*t*, 535
  aortic aneurysms caused by, 37
  aortic arch, 28, 118
  hypertension as risk factor for, 103, 118
  intracranial, 113, 118
  stroke caused by, 28–31
  transient ischemic attacks caused by, 28–31
Atherosclerotic disease, 43
  and coronary artery disease, 47
Atherosclerotic plaque in aortic arch, 118
Atlantoaxial subluxation
  brainstem compression caused by, 895
  cervical myelopathy caused by, 364–365, 391, 895
Atlanto-occipital subluxation, 391
Atovaquone, for malaria, 827
ATP7B protein, 211
Atrial cardiopathy, 70
Atrial fibrillation (AF), 65–66, 69–72, 79. *See also* Arrhythmia, cardiac; Atrial flutter
  after cardiac surgery, 79, 974
  anticoagulant therapy for, 78–79
  antithrombotic therapy for, 75
  cardioversion of, 72
  echocardiographic features of, 71–72
  hyperthyroidism and, 299
  ischemic stroke as cause of, 164
  lone, 69
  pathogenesis, 70
  pathophysiology, 70
  prevalence of, 69
  risk factors for, 69
  risk stratification, 70–72
  secondary AF, 69
  sleep apnea and, 925, 937
  and stroke, 70–71, 173
  warfarin for stroke prevention in, 78*t*, 259
Atrial flutter. *See also* Arrhythmia, cardiac; Atrial fibrillation (AF)
  cardioversion in, 72
  thromboembolism in patients with, 69–70

Atrial myxoma, 73
Atrial septal aneurysm, 73, 80–81
Atrioventricular block, 92
Atrium, left, 69–73
  atrial fibrillation and flutter, 69–72
    cardioversion, 72
    pathophysiology, 70
    risk stratification, 70–72
  atrial myxoma, 73
  sinoatrial disorder, chronic, 72–73
Atrophic gastritis, 237
Atrophic papulosis, malignant, 348*t*, 351
Atropine, 436, 594, 608, 616, 657, 973–974
Attention deficit hyperactivity disorder (ADHD), 61–62
Attenuated vaccines, 854
Atypical antipsychotics. *See also* Antipsychotics
  for agitation prevention in dementia patients, 1107
  hyperthermia and, 666*t*
  for insomnia, 920
  tardive dyskinesia and, 1026
Atypical neuroleptics, 606
Auditory neuropathy, 401
Aura, migraine with, 1047–1050
Autoantibodies
  anti-CCP, 894
  antisynthetase, 898
  in cancer-associated retinopathy, 513
  seizures and, 1015*t*
  in systemic lupus erythematosus, 887
Auto-CPAP devices
  for obstructive sleep apnea, 926
Autoimmune autonomic ganglionopathy, 547
Autoimmune diseases, 791. *See also* Paraneoplastic syndromes; *individual disorders*
  epilepsy and, 1015–1016
  and headache, 1052
  myoclonus and, 1034
  otoneurologic manifestations of, 407
  parkinsonism and, 1044–1045
Autoimmune encephalitis following herpes simplex encephalitis, 761
Autoimmune inflammatory meningoencephalitis, 1034
Autoimmune meningoencephalitis, 460
Autoimmune neuropathies, gut dysmotility and, 230–231
  antibodies to ganglionic acetylcholine receptors, 230
  antibodies to specific ion channels, 230–231
Automated oscillometric blood pressure devices, 103
Autonomic epilepsy, 226
Autonomic function tests. *See* Postural hypotension, autonomic function evaluation
Autonomic hyperreflexia
  characteristics of, 127, 569
  definition of, 127
  in pregnancy, 594
  signs and symptoms of, 594
Autonomic nerves, 33
Autonomic neuropathy, 128, 230. *See also* Baroreceptor reflexes; Dysautonomia; Postural hypotension; Syncope; *specific disorders*
  aortic disease as cause of, 33–35
    anatomy, 33–34
    postsympathectomy neuralgia, 34
    sexual function, disorders of, 34–35
  chronic, 230
  diabetes mellitus and, 128, 228–229, 312–314, 972
  diarrhea in, 223
  investigations of, 133–140, 312–314
  in leprosy, 732
  paraneoplastic, 129, 517
  postural hypotension secondary to, 125, 129
  pupillary effects of, 312
  Sjögren syndrome and, 892
  uremic, 257
  vincristine and, 525–526
Autonomic system degenerations, gut dysmotility and, 227
  idiopathic orthostatic hypotension, 227
  multiple system atrophy, 227–228
  pandysautonomias/selective dysautonomias, 227
  postural orthostatic tachycardia syndrome, 227
Autonomous neurogenic bladder, 546
Autonomy, of patient, 154, 1112–1114, 1119, 1121
Autophagic myopathies, 624
Autoregulation, 102, 104–105
Autovagotomy, 229
Axillary puncture, 961
Axonal neuropathy, 33, 205–206, 243, 256, 295, 357, 386, 466, 517, 526, 617, 649, 657, 781, 870, 878, 892, 1069, 1074
  acute motor, 1068–1069
  acute motor-sensory, 1069–1070
  distal, 649
  vaccination and, 856*t*
Axonal polyneuropathy, 1064*t*, 1073
Azathioprine, 506*t*, 783, 798*t*, 799, 848, 1069
  for chronic inflammatory demyelinating neuropathy, 597, 1070
  for inflammatory bowel disease, 206
  for Lambert–Eaton myasthenic syndrome, 1076
  for multifocal motor neuropathy, 1067
  for myasthenia gravis, 973
  myoglobinuria, 1083*t*
  for myositis, 1080
  for neuromyelitis optica, 514
  for polychondritis, 394
  for sarcoidosis, 848, 882
  for systemic lupus erythematosus, 889
  for vasculitis, 899, 902

B

B cells, 501–502
Bacille Calmette-Guérin (BCG) vaccination, 728
Back pain
  in epidural spinal cord compression, 486
  nonsteroidal anti-inflammatory drugs for, 391
  in Paget disease of bone, 385
  in pregnancy, 594–595
  in tuberculous osteomyelitis, 389
  in vertebral osteomyelitis, 387
Baclofen, 432–433, 506*t*, 515, 572*t*, 605, 605*t*, 608–611, 613, 615–616, 967, 1021, 1024, 1026–1027, 1033, 1038
Bacterial brain abscess, 693
Bacterial endocarditis, 179
Bacterial infection in post-transplantation period, 788
Bacterial meningitis
  antimicrobial therapy for, 688–689, 688*t*
  bacteria that cause, 683–684
  cerebrospinal fluid findings in, 685
  in children, 692
  clinical presentation of, 684–685
  as complication of myelography, 958
  definition of, 683
  dexamethasone for, 690–692
  diagnosis of, 685–686

  differential diagnosis of, 686–688
  etiology of, 683–684
  focal infectious intracranial mass lesions, 688
  increased intracranial pressure in, 684
  in infants, 692, 696
  lumbar puncture in, 685
  meningismus in, 684–685
  meningococcal, 689–690, 689*t*, 692
  meningococcemia and, 685
  neurologic complications of, 691*f*
  organisms that cause
    Enterobacteriaceae, 684, 690
    Listeria monocytogenes, 683, 690, 787
    Neisseria meningitidis, 683
    Pseudomonas aeruginosa, 690
    Staphylococcus aureus, 683
    Streptococcus agalactiae, 683
    Streptococcus pneumoniae, 683–685, 692
  pneumococcal, 684, 689, 692
  polymerase chain reaction in, 685
  prevention of, 692
  seizures in, 684
  staphylococcal, 690
  and stroke, 179–180
  treatment of, 688–692, 688*t*
  viral meningitis, 686
Balamuthia infection, 831
Balamuthia mandrillaris, 822*t*
Balint syndrome, 423–424
Ballism, 1023–1033
Balloon atrial septostomy in neonates with TGA, 56
Bannwarth syndrome, 845
Barbiturates, 608, 1010–1011
  coma caused by, 989
  hyperthermia and, 666*t*
Bariatric beriberi, 202
Bariatric surgery, 201–202
Barium videofluoroscopy, 219–221
Baroreceptor activity, 158
Baroreceptor reflexes, 123
  aortic, 126
  carotid, 126
  postural responses by, 127
  sensitivity, 135, 165
Baroreflex receptor sensitivity, 125
Barotrauma, 411
Barraquer–Simons syndrome, 369
Bartholin glands. *See* Greater vestibular glands
Bartter syndrome, 270
Basal ganglia encephalitis, 508–509
Basedow paraplegia, 295
Bassen–Kornzweig disease, 208, 446–447
Batson plexus, 482, 490, 496
Baylisascaris disease, 835–836
Baylisascaris procyonis, 835–836
B-cell depletion, 593
B-cell malignancies, 790
Becker muscular dystrophy, 231
Bedside spirometry, 7
Behavioral therapy
  for delayed sleep phase disorder, 928
  for insomnia, 918
Behçet syndrome, 904–906
  antiphospholipid antibodies in, 350–351
  central nervous system manifestations of, 906, 1041, 1044–1045
  diagnostic criteria for, 904
  headache in, 906
  increased intracranial hypertension in, 906
  inflammatory brain disease in, 812*t*
  magnetic resonance imaging of, 906
  movement disorders in, 1030–1031, 1044–1045
  neurocutaneous manifestations of, 352*t*, 355–356, 368–369
  nonparenchymal, 906
  otologic symptoms in, 408
  peripheral nervous system manifestations of, 906
  systemic manifestations of, 904–905
  treatment of, 906
Belimumab, for systemic lupus erythematosus, 889
Bell palsy, 310–311, 327–328, 405–406, 406*f*, 596
Bence Jones protein, 1071
Benign paroxysmal positional vertigo (BPPV), 401, 403*f*, 432
Benign tumors of nerves, 1063–1064
Benzhexol, and parkinsonian symptoms, 612
Benzodiazepines, 45, 608, 889–890, 1010–1011, 1024, 1051–1052
  akathisia and, 609
  for alcohol withdrawal seizures, 628–629, 668, 1019
  for arousal disorders, 934
  for delirium tremens, 628, 668–669
  drug-induced coma and, 607
  encephalopathy and, 606, 608
  for insomnia, 918–920, 919*t*
  hallucinatory states and, 608
  hepatic encephalopathy and, 197, 1010–1011, 1089–1090
  hepatic porphyria and, 1017
  hyperprolactinemia and, 331*t*
  hypotension caused by, 1012
  hypothermia and, 667*t*
  mood disorders and, 608
  movement disorders and, 1026, 1029*t*, 1031–1034, 1036*t*, 1039
  pharmacokinetics of, 1009*t*
  and postoperative delirium, 969, 981
  seizures and, 606, 628, 641, 988, 1012, 1017, 1021
  serotonin syndrome and, 967
  side effects of, 612, 615, 641, 920
  for spasticity, 967
  stiff person syndrome, 515
  traumatic brain injury, 166
Benztropine, and parkinsonian symptoms, 612
Beriberi, thiamine deficiency and, 243, 1071–1072
Berlin Heart EXCOR ventricular assist device, 57–58
Bernard–Soulier syndrome, 463
Beta-1 adrenergic receptors, 158
β_2-microglobulin amyloidosis, 261
Beta-3 receptor agonists, 554
β-amyloid deposition, 892
Beta-blocker initiation and postoperative stroke, 50
β-blockers, 168, 1049, 1051, 1053*t*
  for cardioprotection, 168
  hyperthermia and, 666*t*
β-interferon therapy during pregnancy, 593
Beta-receptors, 160
Bevacizumab, 420, 522*t*, 528, 533, 606, 621*t*
Bezold–Jarisch reflexes, 133
Bilevel positive airway pressure
  for obstructive sleep apnea, 926
Bing Neel syndrome, 451
BioFire PCR Film Assay, 807
Bioprosthetic heart valve, 76, 91, 96
  embolus prevention and, 50
Biotinidase deficiency, 362*t*
Bisacodyl, 227–228

Bisphosphonates, for Paget disease of bone, 384–385
Bitemporal hemianopia, 329
Bladder
  incomplete emptying of, 544
  innervation of, 542, 543*f*
  neurogenic. *See* Neurogenic bladder
  neurologic control of, 541–544
  overactive, 543, 545–546, 548, 552–555, 572*t*
  pharmacology of, 542–544
  in storage phase, 542
  urothelium of, 542–544
  in voiding phase, 542
Bladder catheters, in dementia, 1109–1110
Bladder diary, 548, 549*f*
Bladder dysfunction
  amyloid neuropathy and, 547
  autoimmune autonomic ganglionopathy and, 547
  basal ganglia lesions and, 545
  brainstem lesions and, 545
  cerebral lesions and, 545–546
  diabetic neuropathy and, 546–547
  drug-induced, 616
  Fowler syndrome, 547–548
  Guillain–Barré syndrome and, 547
  immune-mediated neuropathies and, 547
  multiple system atrophy and, 545
  myotonic dystrophy and, 547
  neurogenic, 544–548
  Parkinson disease and, 545
  peripheral neuropathies and, 546–547
  pure autonomic failure and, 547
  spinal cord lesions and, 545–546
  types of, 544*t*, 545
Bladder neuropathy, 312
Bladder scan, 548
Blast-induced trauma, 411
Blastomyces dermatitidis, 804*t*, 808–809
Blastomyces dermatitis, 790
Blastomycosis, 352*t*, 808
Blastomycotic meningitis, 808
Bleeding disorders and maternal epilepsy, 579–580
Blindness
  in cryptococcal meningitis, 817
  from onchocerciasis, 836
Blindness, cortical, 44–45, 121, 148, 356, 523, 526–527, 606, 615
Bloch–Sulzberger disease, 360–361, 361*f*
Blood lipids and stroke, 115–116, 118, 172, 175, 363, 975, 1011
Blood pressure. *See also* Hypertension; Hypotension
  postural changes effect on, 124, 124*f*, 134
Blood viscosity, reduction of, 47–48. *See also* Hyperviscosity; Cellular hyperviscosity
Blood volume, effective, 125
Blood–brain barrier (BBB), 91*f*, 102, 197, 199, 208, 243, 327, 363, 467–468, 477, 485, 492, 501, 531–532, 554, 605, 645, 690–691, 691*f*, 703–705, 707, 713, 741, 770–771, 804, 806, 809, 878, 971, 994, 1089, 1103
Blow-out fracture with muscle entrapment, 425*t*
B-lymphocyte hyperactivity, 890
Body mass index, narcolepsy and, 921
Boeck, Caesar, 867
Bone disease
  ankylosing spondylitis, 389–392, 390*f*
  diffuse idiopathic skeletal hyperostosis, 391–392
  osteogenesis imperfecta, 408–409, 409*f*
  osteomalacia. *See* Osteomalacia
  osteopetrosis, 381–384, 384*t*. *See also* Osteopetrosis
  osteoporosis. *See* Osteoporosis
  otoneurologic manifestations of, 408–409
  Paget disease of bone. *See* Paget disease of bone
  tuberculous osteomyelitis, 388–389
  vertebral osteomyelitis, 387–389, 388*f*
Bone marrow transplantation, 445, 466, 508, 792, 1042, 1073
Bone metastases, 475, 485, 488, 1059
Borderline leprosy, 731, 732*f*
Bordetella pertussis, 860
Borrelia afzelii, 708
Borrelia burgdorferi, 1059
  description of, 353–354
  Lyme disease caused by, 352*t*, 353–354, 354*f*, 406, 710–714, 712*t*–714*t*, 845, 901, 1024, 1029*t*, 1037, 1059, 1091. *See also* Lyme disease
  lymphocytic meningitis caused by, 748
Borrelia lymphocytoma, 710
Bortezomib, 451, 522*t*, 528, 617
Botulinum toxin, 298, 386, 553–555, 556*t*, 610, 619–620, 620*t*, 752, 1028, 1033, 1041, 1074, 1075*t*, 1109, 1121
  for neurogenic bladder storage dysfunction, 554–555
Botulism
  diagnosis of, 1075
  food-borne, 1074–1075
  infant, 1074
  pathogenesis of, 1074–1075
  postural hypotension in, 131
  treatment of, 1075
  wound, 642, 1074
Bovine spongiform encephalopathy, 759
Brachial diplegia, 148
Brachial plexopathy
  after cardiac surgery, 45
  description of, 493–494
  immune, 1061, 1066*t*
  inflammatory bowel disease and, 205, 205*t*
  Lyme disease and, 712
  metastases and, 327, 493–495, 1061
  in pregnancy, 595
  radiation induced, 524, 534, 534*t*, 1061–1062
  vaccine and, 856*t*, 861
  West Nile virus and, 1059
Brachydactyly mental retardation syndrome, 366*t*
Bradyarrhythmias, 83
Bradykinesia, 191, 193, 509, 545, 548, 567, 611, 655, 936, 985, 1038, 1042–1045, 1100–1102
Bradykinin, 130
BRAF inhibitors, 481, 482*t*, 492
Brain abscess
  antimicrobial therapy for, 695
  bacterial, 693
  in cerebritis stage, 695
  in children, 693
  clinical presentation of, 696–697
  as complication of infective endocarditis, 59–60, 76–77
  corticosteroids for, 695
  in cyanotic congenital heart disease, 693
  definition of, 692–693
  dental disease and, 695*t*
  diagnosis of, 694, 811
  differential diagnosis of, 694
  endocarditis and, 692–693, 695*t*
  etiology of, 693
  head trauma and, 692–693, 695*t*
  headache in, 693
  in infants, 693
  in infective endocarditis, 87–91, 89*f*, 94–95, 97
  lumbar puncture and, 694

  magnetic resonance imaging of, 693–694
  metastatic, 693
  middle ear infections and, 693
  neonatal, 693
  neurosurgical procedures and, 692–693, 695t
  Nocardia asteroides, 692–693
  organisms that cause, 693
  from paranasal sinuses, 693, 695t
  pulmonary disease and, 695t
  seizures in, 693
  stereotactic needle aspiration of, 694
  transplantation and, 267–270
  treatment of, 694–695, 695t
Brain and skull tumors, headaches and, 1052
Brain death, 49, 1096t, 1097, 1097f
Brain diseases, gut dysmotility and, 225–227
  Alzheimer disease, 225
  amyotrophic lateral sclerosis, 226
  autonomic epilepsy and migraine, 226
  brainstem lesions, 227
  head injury, 226
  migraine, 226
  parkinsonism, 225–226
  postpolio dysphagia, 226
  stroke, 225
Brain metastases
  chemotherapy for, 481
  clinical features of, 476–477
  diagnostic studies of, 477–478, 477f
  differential diagnosis of, 478
  epidemiology of, 476
  hematogenous dissemination of, 476
  immunotherapy, 481
    ipilimumab, 481
    nivolumab, 481, 482t
    pembrolizumab, 481
  molecular genetic analysis, 476
  neurologic manifestations of, 476–477
  pathology of, 476
  pathophysiology of, 476
  prognostic variables
    Disease-Specific Graded Prognostic Assessment (DSGPA), 478–479
  prognostic variables for, 479–482
  prophylactic cranial irradiation for, 481–482
  small cell lung cancer, 481–482
  solitary, 477f
  stereotactic radiosurgery, 480–481
  supportive treatment of, 479
  surgery for, 479–480, 480t
  targeted therapies for, 481
  treatment of, 479–482
  whole-brain radiotherapy for, 480, 480t
Brain tumors
  endocrine dysfunction in long-term survivors of, 300–301
  intracerebral hemorrhage caused by, 109
  respiratory dysfunction associated with, 16
  transplantation and, 265–266, 265f, 268f
Brain–pituitary–gonadal axis, 317–318, 318f
Brainstem
  encephalitis of, 433, 503t, 508–509, 512, 864, 1044
  encephalopathy of, 532
  lesions of
    gut dysmotility and, 227
    postural hypotension caused by, 127
  tumors of, respiratory dysfunction caused by, 16
Brainstem auditory evoked potentials
  and cisplatin, 614
  hypothermia and, 667, 669
  in neurosarcoidosis, 878
  in organic solvent exposure, 651–652
Brainstem respiratory centers, disorders of, 4, 5f, 9, 17t, 327
Branch retinal artery occlusion, 420t
Branched-chain amino acids, 198
Breast cancer, 264, 279, 318, 322, 324, 510–513, 515, 530, 534, 605, 617, 897, 1061, 1081
  brain metastasis from, 477f, 479, 481, 482t, 483t, 489, 491–492
  dural metastases from, 485f
  epidural spinal cord compression and, 487f
Breast-feeding, 580, 589, 591, 593
  carpal tunnel and, 596
  and maternal epilepsy, 580
  and myasthenia gravis, 598
  and traumatic paraplegia, 594
Breathing, 4–6
  apneustic, 8
  apraxia, 9
  ataxic, 8
  chemical control, 4
  Cheyne–Stokes, 8, 10, 17
  cluster, 10
  control of, 4–6, 5f
  disordered, with sleep, 6–7, 16–17, 924–927. *See also* Sleep apnea; Sleep hypoventilation syndrome; Sleep-related breathing disorders
    central sleep apnea (CSA) syndromes, 16–17
    respiratory dysrhythmias, 17
    sleep hypoventilation syndrome, 17, 17t
    sudden infant death syndrome, 17
    upper airway obstruction, 16
  dysfunction, from neurologic disorders, 10–16
  factors influencing the control of, 6
  forebrain's role in, 6
  mechanical inputs and, 4–5
  patterns of, 7–10
  peripheral chemoreceptors and, 4
  respiratory rhythm pattern generators, 4
  voluntary control, 5–6
Brill–Zinser epidemic typhus, 352t
Bromides, 608
Bromocriptine, 11, 166, 319, 326, 331, 604, 605t, 608, 610, 613–614, 667t, 668, 966, 985, 1027t, 1035
  hypothermia and, 667t
Bronchodilators, 605t, 917t, 1051
Brown-Séquard syndrome, 489, 533, 891
Brudzinski sign, 684–685
Brugada syndrome, 83–84
Brun nystagmus, 432
Bruns–Garland syndrome. *See* Diabetic lumbosacral plexopathy
Bruton tyrosine kinase, 454
B-type natriuretic peptide (BNP), 163
Bubonic plague, 353t
Buffalo Concussion Exercise Treatment Protocol, 678
Bulbocavernosus reflex, 552, 570–571
Bumetanide, 411
Bupropion, 1020
Burkitt lymphoma, 453–454
Burst neurons, 427
Butyrophenones, 609–610
  hyperthermia and, 666t
Bypass conduits, 43
Bystander activation, 855

C

- C1–C2 puncture
  - complications of, 957
  - description of, 955–956
  - epidural injection during, 957
  - indications for, 957
- CA1 neurons, 148
- Cabazitaxel, 522*t*, 525, 617, 617*t*
- Cabergoline, 331
- Cachectic myopathy, 1005
- Cactus morphology, 71–72
- CADASIL. *See* Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- Café-au-lait spots, 344, 346*f*
- Caffeine, 986
- Caffeine withdrawal, 970
  - and headache, 1051
- Calcineurin inhibitors, 786–787, 795, 797–798, 798*t*. *See also* Cyclosporine; Tacrolimus
  - hypertension caused by, 797
  - neurologic complications of, 797
  - and peripheral nervous system, 797
  - seizures and, 797
  - tremor and, 797
- Calciphylaxis, in end-stage kidney disease, 258
- Calcitonin, 278, 319, 337, 378, 384–385, 409, 685, 1039*t*
- Calcium
  - disturbances of, 278–279, 1019–1020
  - hypercalcemia, 279, 335*t*, 337, 381, 450–451, 500*t*, 868*t*, 877, 883, 968*t*, 1019, 1040, 1089*t*, 1090
  - hypocalcemia, 278–280, 338, 380–384, 500*t*, 591, 796, 971, 997*t*, 1005, 1008
- Calcium channel blockers, 103, 121, 127, 168, 584, 610–611, 612*t*, 621, 624, 931, 1012, 1026, 1027*t*, 1042, 1050, 1052–1053, 1053*t*, 1075–1076
- Calcium channels, 294, 314–315, 932*t*
- California encephalitis virus, 743*t*, 746
- Canadian Pediatric Ischemic Stroke Registry, 57
- Cancer. *See also* Chemotherapy; *specific cancer*
  - chemotherapy for, neurologic complications of, 522–530
  - consciousness affected by, 1091
  - direct tumor effects, stroke and, 182
  - immunotherapy, 529
  - paraneoplastic effects, on nervous system, 499
  - radiation, neurologic complications of, 530–536
  - retinopathy associated with, 513
  - seizures associated with, 1018–1019
- Cancer, coagulation disorders in
  - and stroke, 181
- Cancer therapy, stroke related to, 182
- *Candida*, 77, 91–92, 387. *See also Candida* spp.
- *Candida* spp., 92, 618, 792, 804–805, 804*t*, 809–810, 812*t*, 843–844
  - diagnostic testing, 843–844
  - meningitis caused by, 804–805, 810, 812*t*, 813–814, 817–818, 842–844
- Cannabidiols (CBD), 1011
- Cannabinoids, 185, 315, 554, 606, 645, 666*t*
  - hyperthermia and, 666*t*
  - for neurogenic bladder storage dysfunction, 554
  - and stroke, 185
- *Cannabis sativa*, 1011
- Caplacizumab, 466
- *CAPN3* mutations, 457
- Captopril, 608, 612*t*, 615, 617–619
- Carbamate pesticides, 656–658, 1075*t*
- Carbamazepine, 479, 566, 606, 971, 1012, 1014*t*, 1017, 1028, 1036*t*, 1037, 1052–1053
  - adverse effects, 320, 336, 336*t*, 373, 566, 572*t*, 581, 606, 609, 611–612, 615, 936, 1011–1012, 1016–1017, 1026, 1027*t*, 1036, 1039*t*, 1052
  - aseptic meningitis and, 604, 748, 840, 850
  - Fabry disease and, 267, 1073
  - fetal malformations and, 579
  - hyponatremia and, 336, 336*t*, 373, 606
  - for neuromyotonia, 506*t*
  - oral contraceptive failure, 320, 581
  - pain and, 495, 575, 596
  - pharmacokinetics of, 1009*t*
  - pregnancy and, 321, 578–580
  - sexual function and, 566, 572*t*
  - superior oblique myokymia, 433
  - thyroid disorder and, 291, 1019
  - for trigeminal neuralgia, 386
  - uremic encephalopathy and, 255
- Carbon dioxide narcosis, 287, 1089–1090
- Carbon disulfide, 652, 1036*t*, 1042, 1064*t*
- Carbon monoxide poisoning, 1025, 1027*t*, 1036*t*, 1042, 1048*t*, 1083*t*
- Carbon-coated beads (Durasphere), 225
- Carbonic anhydrase II deficiency, 383
- Carboplatin, 411, 482*t*, 522*t*, 523*t*, 527–528, 617, 617*t*
- Carcinoid syndrome, 125, 500*t*
- Carcinoid tumor, 223*t*, 229, 238, 339*t*, 340, 495
- Carcinomatous meningitis, 490, 722, 722*t*, 812*t*, 813*t*, 1018, 1037, 1059
- Card agglutination trypanosomiasis test, 829
- *CARD9* gene, 810
- Cardiac arrest
  - anaerobic glycolysis after, 147
  - apoptosis after, 148
  - ethical considerations, 154–155
    - accurate prognostication, 154
    - discussion with surrogate decision-makers, 154–155
  - hypoxic-ischemic encephalopathy after, 147–148
  - neurologic examination after, 150–151
  - "post-arrest syndrome", 147
  - prognostic determination, 148–154
    - biomarkers, 153–154
    - electrophysiologic tests, 151–152
    - multimodal prognostication algorithms, 154
    - neuroimaging, 152–153
    - specific features of, 151
    - targeted temperature management and, 150–151
  - status epilepticus after, 152
- Cardiac calsequestrin gene, 83
- Cardiac causes of ischemic stroke, 69–77
  - atrial myxoma, 73
  - chronic sinoatrial
    - disorder, 72–73
  - endocarditis, 76–77
    - infective, 76–77
    - marantic, 77
  - left atrium, 69–73
    - fibrillation and flutter, 69–72
      - cardioversion, 72
      - pathophysiology, 70
      - risk stratification, 70–72
  - left ventricle, 74–75

    acute myocardial infarction, 74
    cardiomyopathies, 74–75
    dysfunction, 75
  paradoxical embolus, 73
  valvular diseases, 75–76
    aortic valve stenosis, 76
    lambl excrescences, 76
    mitral annular calcification, 75
    mitral valve prolapse, 66*t*, 69, 75
    mitral valve regurgitation, 75
    mitral valve stenosis and rheumatic heart disease, 76
    prosthetic heart valves, 76
Cardiac cephalalgia, 1049
Cardiac disease. *See also* Cardiac arrest; Cardiac causes of ischemic stroke; Cardioembolic stroke
  use of antiseizure medications in, 1012
Cardiac innervation, 160
Cardiac manifestations of neurologic disease, 157–169
  anatomy and physiology, 158–159
    insular cortex, 159
    limbic system and amygdala, 159
    medullary control, 158
    paraventricular nucleus, 158
  cardiac evaluation, 166–167
  catecholamine surge and, 160–162
  clinical management, 167–168
  epilepsy and, 165–166
  of focal neurologic injury, 163–164
    cardiac rhythm, disturbances of, 164–165
    electrocardiographic findings, 163–164, 164*f*
  of global neurologic injury, 162–163
    B-type natriuretic peptide (BNP), 163
    cardiac biomarkers, 162
    creatine kinase (CK)-MB, 162
    reduced left ventricular function, 162
    regional wall motion abnormalities, 162
    troponin, 162–163
  historical perspective, 157–158
  mechanism of, 160–162
  traumatic brain injury, 166
Cardiac myocytolysis, 157–158
Cardiac rhythm disturbances. *See* Arrhythmia, cardiac; Atrial fibrillation (AF); Atrial flutter
Cardiac ryanodine receptor, 83
Cardiac RYR-2 ryanodine receptor, 158
Cardiac sarcoidosis, 81–82
Cardiac surgery
  atrial fibrillation after, 79, 974
Cardiac surgery, neurologic complications of, 43
  cardiac transplantation, 51–52, 795–796
  cardiac valvular surgery, 49–50
  choreoathetosis after, 60, 1025
  coronary artery bypass grafting, 43–46, 50–51
    nonstroke neurologic complications after, 45–46
    stroke after, 44–45
  extracorporeal circulation, 46–49
  extracorporeal membrane oxygenation (ECMO), 48–49
  preoperative prevention, 50–51
  visual disorders associated with, 984
Cardiac syncope, 81–82, 132
Cardiac transplantation, 51–52, 795–796
Cardiac troponin I, 162
Cardiac valvular surgery, neurologic sequelae of, 49–50
Cardioembolic stroke, 44, 57–58, 65–69, 74, 76, 164, 298
  atrial fibrillation and, 70, 78–79, 173, 298
  cardiac valve disease and, 75–76, 173
  cardiomyopathy and, 74–75, 80
  clinical features, 67, 67*t*
  after coronary artery bypass grafting, cortical signs in, 67
  echocardiography, 68–69
  electrocardiographic (ECG) monitoring, 69
  emergency reperfusion treatment, 77–78
  endocarditis and, 76–77, 89*f*, 91, 98, 113, 181, 348*t*
  endovascular therapy, 78
  homocystinuria and, 350
  imaging, 67–68
  investigations, 67–69
  left atrial myopathy and atrial fibrillation as mechanisms of, 71*f*
  management, 70, 77–81
  mechanisms of, 70–77, 71*f*
  and myocardial infarction, 74, 80
  oral contraceptives and, 319
  and patent foramen ovale, 80–81, 474
  perioperative, 974–975, 974*t*
  thrombolysis, 77
  stroke prevention, 78–81
  systemic lupus erythematosus and, 890
  Takayasu arteritis and, 904
  thrombolysis, 77
  treatment decisions, 79–80
  vasculitis and, 393
Cardiofaciocutaneous syndrome, 366*t*
Cardiomyopathies, 74–75, 583
  alcohol-induced, 184, 634–635
  associated neurologic manifestations, 84
  atrial fibrillation and, 69
  Chagas disease, 74
  cocaine-induced, 637–638
  definition of, 74
  dilated, 74–75, 179*t*, 380, 447, 773
  Fabry disease and, 186
  HIV and, 773
  hypertrophic, 74, 81, 124, 184
  ischemic, 83
  and left ventricular dysfunction, 80
  methamphetamine-induced, 639
  muscular dystrophies and, 972–973
  peripartum, 584
  pregnancy and, 174
  primary, 74
  sarcoid-associated, 875
  secondary, 74
  stress-induced, 157–158
  Takotsubo, 161–162
Cardiopulmonary bypass, 56–58
  extracorporeal circulation circuit in, 46–48, 47*f*
  extracorporeal circulation, neurologic complications of, 48–49
  neurologic complications of, 44, 46–47, 47*f*, 51*t*, 60–62, 974–976
  pituitary apoplexy and, 44
  platelet function and, 463
  temperature changes and, 669–670, 1025
Cardiopulmonary bypass machine, 43
Cardiopulmonary resuscitation, 151–152, 1033, 1114–1115
Cardiopulmonary stretch receptors, 126
Cardiovascular disease
  and headache, 1049
  and postural hypotension, 124–125
Cardioversion, for atrial fibrillation, 66*t*, 72, 925
Carfilzomib, 528, 617

Carotid artery
  angiography, 106, 116, 959–960
  radiation-induced vasculopathy of, 182
  stenosis of
    cervical bruit and, 51, 116, 976
    diagnostic imaging of, 116
    historical investigations of, 115
    hypertension as risk factor for, 115–117
    lacunar infarct risks, 111–113
    stroke risks, 115, 116*t*
    surgical treatment of, 116–117
Carotid atherosclerosis, chronic kidney disease and, 258
Carotid bodies, 4
Carotid bruits, 51, 116, 976
Carotid Doppler ultrasonography, 116
Carotid endarterectomy, 51, 116–117, 259, 962, 974–976
Carotid revascularization technique, 51
Carotid sinus reflex, hypersensitive, 133
Carotid sinus syncope, 133
Carotid stenting prior to CABG, 51
Carpal tunnel syndrome, 138, 202, 205–206, 210, 261, 279, 291, 295, 308–309, 327, 331, 357, 368, 450, 595, 889, 893, 896–897, 903, 1064–1065, 1068
  characteristics of, 308
  conservative management of, 1064–1065
  diabetes mellitus and, 308–309
  dialysis and, 261
  hypothyroidism and, 291, 1068
  management of, 1065
  medical conditions associated with, 1064–1065
  polymyalgia rheumatica and, 903
  in pregnancy, 595
  rheumatoid arthritis and, 896
  risk factors for, 1064–1065
  Sjögren syndrome and, 893
  systemic lupus erythematosus and, 889
  Tinel sign for, 308
CASPR2 antibodies, 507, 519
Catamenial epilepsy, 321
Catamenial migraine, 318
Catamenial sciatica, 327
Cataplexy
  narcolepsy with, 920–921
  treatment of, 922, 922*t*
Catatonia, 889–890
Catecholamine polymorphic ventricular tachycardia (CPVT), 158
Catecholamine surge, 159–160
  on cardiomyocytes, 160
  on coronary microvasculature, 161–162
Catecholaminergic polymorphic ventricular tachycardia, 83
Catecholamines, 161–162, 165, 294, 378, 594, 966
  adrenal medulla and, 339–340
  -induced subendocardial lesions, 160
  in neurocardiogenic injury, 168
  polymorphic ventricular tachycardia induced by, 83
  subendocardial lesions induced by, 160
Cauda equina
  compression of, 486, 799
  lesions of
    sexual dysfunction in, 569–570
    sphincter electromyography evaluations, 551–552
  neurogenic claudication of, 376–377
Cauda equina syndrome, 391, 782, 983*t*, 984, 988, 1059
Cavernomas, radiation-induced, 535, 536*f*
Cavernous malformations, 108, 110, 110*f*, 348*t*
Cavernous sinus, 309, 328–329, 330*t*, 333, 427–429, 434, 449–450, 484, 700, 871, 873, 892
  anatomy of, 328, 427, 429, 699*f*, 700
  thrombosis of, 330*t*, 333, 456, 471, 700
Cavernous sinus syndrome, 483*t*, 485*f*
CD79B mutation, 454
CDR2, 503*t*, 510
CDR2L, 503*t*, 510
Cefepime, for bacterial meningitis, 688*t*
Cefotaxime
  for bacterial meningitis, 688, 688*t*
  for brain abscess, 694
  for Lyme disease, 714*t*
Ceftazidime, for bacterial meningitis, 688, 688*t*
Ceftriaxone
  for bacterial meningitis, 688*t*
  for Lyme disease, 714*t*
Cefuroxime, for Lyme disease, 714*t*
Celiac disease (CD), 203, 1047
  ataxia, 203–204
  characteristics of, 203
  epilepsy and, 204
  movement disorder associated with, 1031
  myoclonus and, 1034
  myopathy and, 204
  neurocutaneous manifestations of, 362*t*
  neurologic dysfunction associated with, 203
  peripheral neuropathy, 204
  prevalence of, 203
Cellular hyperviscosity, 449
Central apnea, 925
Central auditory processing disorder, 405
Central catecholamine deficiency, 130
Central chemoreceptors, 4
Central core myopathy, 973
Central diabetes insipidus, 334–335
"Central drive" impairment, 998
Central hypoventilation
  acquired, 9
  congenital central hypoventilation syndrome, 9
Central nervous system (CNS), 521, 841. *See also* Spinal cord; *specific brain entries*
  Behçet disease manifestations of, 906
  cardiovascular function regulated by, 126
  demyelination of, 863
  disease, 459
  fungal infections in, 814–817
  hemophagocytic lymphohistiocytosis, 459
  human immunodeficiency virus in
    blood–brain barrier effects on, 770–771
    description of, 766–767
    targeted treatment of, 770–771
  imaging of, 951–962
  neuroborreliosis manifestations of, 710, 712*t*
  organic solvents effect on, 651–652
  paragonimiasis of, 837
  polyarteritis nodosa manifestations of, 900
  primary angiitis of, 898
  rheumatoid arthritis manifestations of, 895–897
  Sjögren syndrome manifestations of, 891–892
  systemic vasculitis manifestations of, 900
  Takayasu arteritis manifestations of, 904
  tuberculosis of. *See* Tuberculosis
  varicella zoster virus invasion of, 752–753
  vasculitis of, 393

Central nervous system (CNS) infections. *See also specific organisms*
  acute bacterial meningitis. *See* Bacterial meningitis
  after cardiac transplantation, 51–52
  brain abscess. *See* Brain abscess
  epidural abscess. *See* Epidural abscess
  fungal. *See* Fungal infections
  post-transplantation, 787
  septic intracranial thrombophlebitis, 699, 699*f*
  stroke and, 792
  transplantation and, 267–270, 270*f*, 791
  viral
    acute hemorrhagic leukoencephalitis, 762
    encephalitis. *See* Viral encephalitis
    meningitis. *See* Viral meningitis
    pathogenesis of, 741–742
    postinfectious complications of, 761–763
    postinfectious encephalomyelitis, 761–763, 762*f*, 763*t*
    transverse myelitis, 762, 763*t*
Central neurogenic hyperventilation, 9
Central pontine myelinolysis, 794
  alcoholism and, 633
  animal models of, 275–276
  hyponatremia and, 275–276, 276*f*, 634
  laboratory findings in, 633
  lesions associated with, 633
  manifestations of, 633
  pseudobulbar palsy associated with, 633
  treatment of, 633
Central retinal artery occlusion, 420*t*
Central scotoma, 44–45, 421–422, 652, 779
Central sleep apnea (CSA) syndromes, 6, 16–17, 326–327, 1101. *See also* Sleep apnea
Central tremor, 1038
Central venous sinus thrombosis (CVST), 906
Central vestibular disorders, 402–405
Central vestibular nystagmus, 432
Cephalosporins, 606, 620
  high doses of, 606
Ceramide trihexosidase, 347–349
Cercariae, 836
Cerebellar ataxia. *See also* Ataxia
  hypothyroidism and, 289
  viruses that cause, 763*t*
Cerebellar degeneration
  alcoholic, 632–633
  Chiari malformation and, 405
  paraneoplastic
    antibodies associated with, 510
    clinical findings of, 509
    description of, 509
    diagnosis of, 512
    history of, 509
    Hu antibody in, 510
    immunosuppressive therapies for, 512
    intravenous immunoglobulin for, 512
    laboratory evaluation of, 509–511, 510*f*
    Ma antibody in, 510–511
    magnetic resonance imaging of, 509, 510*f*
    pathology of, 511
    Purkinje cells in, 511, 511*f*
    Ri antibody in, 510–511
    Tr antibody in, 510
    treatment of, 512
    tumors associated with, 511
    Yo antibody in, 510
Cerebellar hemangioblastoma, 456
Cerebellar hemorrhage, 405
Cerebellar syndromes, 612
Cerebellar tremor, 1041
Cerebellopontine angle
  disorders of, 401
  tumors of, 432
Cerebellum
  abscess of, 693
  dysfunction of
    chemotherapeutic agents and, 523*t*
    in hypothyroidism, 289
    in Wilson disease, 212
Cerebral abscesses
  in infective endocarditis, 97–98
  intravenous drug abuse and, 645
  treatment of, 694
Cerebral amebiasis, 831
  from *Entamoeba histolytica*, 831
Cerebral amyloid angiopathy, 108, 109*f*
Cerebral aneurysms, 106–107, 270, 393
  definition of, 105
  genetic factors, 105
  hypertension and, 105–108
    subarachnoid hemorrhage, 107–108
    unruptured cerebral aneurysms, 106–107
  magnetic resonance angiography of, 106
  prevalence of, 106
  subarachnoid hemorrhage from rupture of, 38*t*, 105, 106*f*, 108
  surgical clipping of, 106
  unruptured, 106–107
Cerebral angiography
  carotid artery puncture in, 960
  neurologic complications of, 959–960
  stroke risks, 959–960
  of vasculitis, 895
Cerebral angiopathy, postpartum, 584
Cerebral arteriovenous malformation, 92*t*, 108, 349, 583, 586–587, 586*f*, 1042
Cerebral atrophy, 533
  cognitive dysfunction and, 312
Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
  hypertension and, 115–117
Cerebral blood flow (CBF), 678
Cerebral cavernous malformations, 348*t*
Cerebral dysgenesis, 60–61, 366*t*
Cerebral edema, 18, 93, 327
  brain abscess and, 695
  cardiac arrest and, 148, 153
  checkpoint inhibitors and, 529
  concussion and, 674, 1088*t*
  contrast reaction and, 952
  diabetes and, 303
  dialysis and, 262, 264, 1008
  eclampsia and, 599
  hypertension and, 119, 121
  hypo- /hypernatremia, 274, 276, 1019
  immune reconstitution syndrome, 806
  immunosuppression and, 799
  intracranial pressure increase, 327, 423*t*
  liver failure, 196–197, 210, 794, 1090
  myxedema and, 288
  neurotoxins and, 640, 653
  parasitic infection and, 833
  radiation and, 532

Cerebral edema (*Continued*)
  seizures and, 459
  stroke and, 165
  tuberculosis and, 721–722, 724
  viral encephalitis and, 742, 759, 762
Cerebral embolism. *See* Cardioembolic stroke
Cerebral embolization in infective endocarditis, 76–77, 89*f*, 91, 98, 113, 181, 348*t*
Cerebral hemorrhage, 59–60, 93, 171
Cerebral infarction. *See also* Cerebral ischemia; Hemorrhage; Ischemic stroke; Stroke
  chemotherapeutic agents associated with, 182
  diabetes mellitus and, 313–314
  L-asparaginase and, 182
  sickle cell disease and, 444
  and vascular dementia, 313–314
Cerebral infection. *See also* Brain abscess; Encephalitis; Meningitis; *specific disorders*
  in infective endocarditis, 97–98
Cerebral ischemia, 18, 47, 171, 182–183. *See also* Cerebral infarction; Hemorrhage; Ischemic stroke; Stroke
  acquired cardiac disease as cause of, 65
  aortic disease as cause of, 28–31
  during cardiac surgery, 51*t*
  generalized, 65
  hypertension and
    acute phase, 104–105
    chronic phase, 104–105
  in sepsis, 995
Cerebral ischemia, aortic disease as cause of, 28–31, 29*f*, 30*f*
  anatomy, 28
  strokes and transient ischemic attacks, 28–31
    atherosclerosis, 29, 29*t*
    subclavian (cerebral) steal, 29–31
    transient emboligenic aortoarteritis, 29
Cerebral malaria, 821–825. *See also* Protozoan infections
Cerebral microbleeds, 94
Cerebral microinfarcts, 1016
Cerebral salt wasting, 336, 759
Cerebral schistosomiasis, 836
Cerebral toxoplasmosis, 776*t*
  asymptomatic, 825
  congenital, 825–826
  cranial imaging of, 826*f*, 827
  diagnosis of, 827
  in immunocompromised patients, 826
  magnetic resonance imaging of, 826*f*, 827
  manifestations of, 825
  pyrimethamine and sulfonamide for, 827
  Toxoplasma gondii as cause of, 825
  transmission of, 825
Cerebral trauma, seizures, and epilepsy, 1021–1022
Cerebral vascular remodeling and chronic hypertension, 102
Cerebral vasculitis, connective tissue diseases and, 1015–1016. *See also specific diseases*
Cerebral vasospasm
  cannabis and, 185
  endovascular embolization for, 964
  management of, 168
  after subarachnoid hemorrhage, 66, 107–108, 167–168, 274–275, 639
Cerebral venous sinus thrombosis (CVST), 121, 171, 174, 182, 206, 259, 303, 356, 422–423, 442, 445, 463, 470–472, 583, 586, 700, 1093
  in children with congenital heart disease, 59
  computed tomography of, 1093
  lumbar puncture and, 1094
  pregnancy and, 121, 586
  protein C deficiency and, 471–472
  protein S deficiency and, 472
  sex hormone-induced hypercoagulability and, 319–320
Cerebral venous sinuses, 699*f*, 700
Cerebral venous thrombosis, 259, 319–320, 445, 471–473, 585–586, 604, 685, 699, 1042
Cerebrospinal fluid (CSF). *See also specific diseases*
  analysis of
    in African trypanosomiasis, 829
    in ankylosing spondylitis, 391
    in arthropod-borne virus encephalitis, 687
    in bacterial meningitis, 685–686
    with brain tumors, 265
    in *Candida* meningitis, 810
    after cardiac arrest, 153–154
    in diabetic neuropathy, 307
    in dialysis dementia, 263
    in disordered consciousness, 1094
    in Epstein–Barr virus infection, 779
    in fungal meningitis, 812
    in granulomatous amebic meningoencephalitis, 830
    in heat stroke, 667
    in herpes simplex virus encephalitis, 750, 759
    in HTLV-associated myopathy/tropical spastic paraparesis, 783
    in human immunodeficiency virus, 771–772, 775
    in hypothyroidism, 287
    in infective endocarditis, 95, 98
    in ischemic stroke evaluation, 95, 179
    in intracranial venous thrombosis, 585
    in Lyme disease, 711, 713
    with meningeal metastases, 447, 491
    in neurolymphomatosis, 496
    in paraneoplastic syndromes, 501, 504, 509–510, 513
    in primary amebic meningoencephalitis, 830, 830*f*
    in relapsing polychondritis, 393
    in sarcoidosis, 878
    in syphilis, 180, 705–706
    in tuberculous meningitis, 720–721
    in uremia, 252–254
    in viral meningitis, 686–687, 748, 758–759
    in West Nile virus encephalitis, 754, 1059
    in Whipple disease, 207–208
  anti-NMDAR antibodies in, 761
  biomarkers, 153
  cytokines in, 690
  diverting shunt for
    fungal infection of, 805, 818
  leakage of, 956
  loculations, 955
  PCR analysis, 207–208
  pleocytosis, 881, 958
  Venereal Disease Research Laboratory, 180, 704–705, 846
Cerebrospinal fluid escape syndromes, 771–772
Cerebrotendinous xanthomatosis, 362*t*, 363, 366*t*
Cerebrovascular disease. *See also* Cerebral infarction; Cerebral ischemia; Ischemic stroke; Stroke
  coronary artery disease and, 166
  dementia and, 1100
  dialysis and, 260–261
  and headache, 1050
  hyperhomocysteinemia and, 172–173, 258, 420*t*, 471–473
  inflammatory bowel disease and, 206
  in pregnancy, 583–588

    - disseminated intravascular coagulation, 586
    - dural arteriovenous fistulas, 587
    - occlusive arterial disease, 583–585
    - occlusive venous disease, 585–586
    - pituitary infarction or hemorrhage, 586
    - spinal arteriovenous fistulas, 587–588
    - subarachnoid hemorrhage, 586–587, 586*f*
  - sexual dysfunction and, 565–566
  - in systemic lupus erythematosus, 888
- Cerebrovascular responsiveness to CO_2, 6
- Ceritinib, 482*t*, 492
- Ceruloplasmin, 211, 213, 236*t*, 241, 322–323, 1041, 1045
- Cervical collars, 895
- Cervical disc disease, 374–375, 375*f*
- Cervical discectomy, 375
- Cervical myelopathy
  - atlantoaxial subluxation from, in rheumatoid arthritis, 895
  - description of, 374
- Cervical plexopathy, 493
- Cervical plexus metastases, 493
- Cervical radiculomyelopathy, 374
- Cervical spinal cord injury, 16
- Cervical spondylosis, 374–375, 374*f*, 545, 957, 1058
- Cestodes
  - cysticercosis, 831–833, 1079
  - echinococcosis, 833–834, 833*f*
  - sparganosis, 833–834
  - types of, 1079
- CGRP monoclonal antibodies, 1053*t*
- $CHADS_2$ score, 70–71, 79–80
- CHA_2DS_2-VASc scale, 70–71, 79–80
- Chagas disease, 74, 128, 179*t*, 223*t*, 352*t*
- Channelopathies, 83, 294, 973, 1001
- Charcot joint, 305, 707
- Charcot–Marie–Tooth disease, 306*t*, 571, 972, 1070
- Checkpoint inhibitors (CPIs), 459–460, 481, 522*t*, 529, 617*t*, 620, 620*t*, 621*t*, 622, 757, 780, 789, 800–801, 1064*t*, 1075*t*
- Chediak–Higashi syndrome, 366*t*
- Chelation therapy, for lead neuropathy, 654
- Chemical meningitis, 798*t*, 799, 813*t*, 840, 850
- Chemotherapy
  - agents used in, neurologic complications of
    - antimetabolites, 522*t*, 523–525
    - bevacizumab, 420, 522*t*, 528, 533, 606, 621*t*
    - bortezomib, 451, 522*t*, 528, 617
    - cabazitaxel, 522*t*, 525, 617, 617*t*
    - carboplatin, 411, 482*t*, 522*t*, 527–528, 617, 617*t*
    - carfilzomib, 528
    - cisplatin, 411, 482*t*, 522*t*, 527–528, 617, 617*t*
    - cytarabine, 121, 492, 512, 522*t*, 523*t*, 524–525, 530, 604, 605*t*, 606, 611–612, 616, 617*t*, 618, 1039*t*
    - DNA-damaging drugs, 526
    - docetaxel, 523*t*, 525, 617, 617*t*
    - fludarabine, 121, 506*t*, 522*t*, 523, 523*t*, 606, 1070
    - gemcitabine, 522*t*, 523*t*, 525
    - ifosfamide, 243*t*, 336*t*, 522*t*, 523*t*, 526, 606, 1036*t*, 1039*t*
    - ixabepilone, 522*t*, 523*t*, 525–526, 617, 617*t*
    - methotrexate, 239, 239*t*, 266, 394, 482*t*, 492, 496, 522*t*, 523–524, 523*t*, 530, 604, 605*t*, 621, 738, 779, 798*t*, 847, 849, 882–883, 889, 892, 897, 899–900, 902, 904, 1018, 1080
    - microtubule agents, 525–526
    - monoclonal antibodies, 528
    - nab-paclitaxel, 522*t*, 523*t*, 525
    - nelarabine, 522*t*, 523*t*, 525
    - oxaliplatin, 522, 523*t*, 527–528, 617, 617*t*
    - paclitaxel, 522*t*, 523*t*, 525, 617, 617*t*, 1064
    - platinums, 527–528
    - retinoids, 522*t*, 528–529, 604, 608, 614
    - rituximab, 528. *See also* Rituximab
    - selumetinib, 522*t*, 528, 621*t*, 625
    - signs of, 523*t*
    - small molecule inhibitors, 528
    - taxanes, 411, 522*t*, 525, 617, 617*t*
    - temozolomide, 482*t*, 492, 522*t*, 523*t*, 526
    - vincristine, 522*t*, 525–526, 526*t*
  - antituberculous, 389, 723–724
  - for brain metastases, 481
  - for epidural spinal cord compression, 489
  - immunotherapy, 529
    - checkpoint inhibitors (CPIs), 459–460, 481, 522*t*, 529, 617*t*, 620, 620*t*, 621*t*, 622, 757, 780, 789, 800–801, 1064*t*, 1075*t*
    - chimeric antigen receptor (CAR) T-cell therapies, 529–530
  - intrathecal, 530
  - for leptomeningeal metastases, 492
  - for metastatic plexopathy, 494–495
  - neurotoxicity of, 521, 522*t*
  - neutropenia caused by, 804–805
  - peripheral neuropathy and, 617
  - stroke related to, 182
  - tremor and, 1039*t*
- Cheyne–Stokes breathing, 8, 10, 17
- Chiari malformation. *See* Arnold-Chiari malformation
- Chiari network, 66*t*, 73
- Chickungunya virus, 755
- Children. *See* Infant(s); Neonates; *specific diseases*
- Chimeric antigen receptor (CAR) T-cell therapies, 459, 529–530, 801
- Chlordecone, 658, 1036*t*
- Chloromas, 447–448
- Chloroquine, 605, 608, 614, 617–618, 620*t*, 621*t*, 624, 898, 1014*t*, 1075*t*, 1077*t*
- Chlorothiazide, 101, 614
- Chlorpromazine, 318, 606, 608, 610–611, 612*t*, 985, 1035, 1049, 1051
- Cholesterol-lowering agents, 618–621
  - myopathies caused by, 620, 622*f*
  - peripheral neuropathy and, 619
- Cholinergic branch, of ascending arousal system, 914
- Cholinesterase inhibitors, 324–325, 430, 597, 607, 657, 969, 1075–1076, 1100–1101
- Chorea, 591, 1023–1033
  - antiphospholipid syndrome and, 351, 470
  - Behçet syndrome and, 1030–1031
  - celiac disease and, 203
  - diabetes and, 304, 1040
  - drug-induced, 609–611, 1026–1028, 1029*t*
  - electrolte disturbance and, 276, 278
  - Hashimoto thyroiditis and, 1031
  - hepatic disease and, 632
  - and Huntington disease, 12, 127, 591
  - hyperthyroidism and, 296, 1031, 1040
  - hypoxemic-ischemic disorders and, 1024–1025
  - magnetic resonance imaging of, 1032
  - in pregnancy, 321–322, 591
  - neuroleptic malignant syndrome and, 612
  - oral contraceptives and, 321–322, 591
  - paraneoplastic syndromes and, 503*t*, 505, 509, 513, 1031, 1045
  - polycythemia and, 456, 1025
  - postpump, 1025
  - Sydenham, 509, 1028, 1044

- Chorea (*Continued*)
  - systemic lupus erythematosus and, 356, 357*t*, 887–888, 1030
  - toxins and, 1025–1026
  - treatment of, 1032–1033
  - tuberculous meningitis and, 1028
  - Wilson disease and, 211
- Chorea gravidarum, 321–322, 591, 1028
- Chorea-acanthocytosis, 208–209, 321–322, 446–447, 1024
- Choreoathetosis. *See* Chorea
- Chorioretinitis, from *Toxoplasma*, 825, 826*f*
- Christmas disease. *See* Hemophilia B
- Chromaffin cells, 338
  - tumors of, 339–340
- Chromosomal disorders. *See individual disorders*
- Chronic granulomatous disease, of childhood, 810
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), 128, 205, 306, 450, 452, 460, 506*t*, 571, 597, 618–619, 634, 781, 797, 841, 856*t*, 972, 1002, 1041, 1063*t*, 1064*t*, 1067, 1070
- Chronic intestinal pseudo-obstruction, 221–222, 223*t*, 226, 228, 231
- Chronic meningitis. *See* Meningitis, chronic
- Chronic peripheral neuropathy, 228–231
  - amyloid neuropathy, 230
  - autoimmune neuropathies, 230–231
  - chronic sensory and autonomic neuropathy, 230
  - diabetes mellitus, 229
  - human immunodeficiency virus (HIV) infection, 230–231
  - neurofibromatosis, 230
  - paraneoplastic neuropathy, 229
  - porphyria, 230
- Chronic progressive hepatic encephalopathy, 192–193
- Chronic sinoatrial disorder, 72–73
- Chronic traumatic encephalopathy (CTE), 673, 679, 1102–1103
- Chronotherapy for delayed sleep phase disorder, 928
- Churg–Strauss syndrome, 368, 408, 900, 1065–1066
- Circadian rhythm
  - homeostatic process and, 914
  - neurobiology of, 914
  - suprachiasmatic nucleus and, 914
- Circadian rhythm disorders, 927–931. *See also* Sleep disorders
  - advanced sleep phase disorder, 928, 929*f*
  - delayed sleep phase disorder, 928*f*
  - diagnosis of, 927
  - irregular sleep-wake disorder, 930, 936
  - jet lag disorder, 914, 930, 930*f*
  - light therapy for, 914
  - pathogenesis of, 927
  - shift work disorder, 929
- Circle of Willis, 68, 88, 178
- Cirrhosis
  - hepatic encephalopathy in, 197–198
  - parkinsonism and, 192–193, 198
- Cisplatin
  - brain metastases and, 482
  - hypomagnesemia and, 280
  - neurologic complications of, 522*t*, 523*t*, 527, 527*t*, 606, 614, 892
  - ototoxicity caused by, 410–411, 527, 614
  - peripheral neuropathy and, 306*t*, 515, 522*t*, 523*t*, 525, 527, 617, 1060*t*, 1063*t*
  - postural hypotension and, 129
- Cisternal puncture, 956
- Citalopram, 612*t*, 769, 1026, 1107
- *Cladophialophora bantianum*, 811
- *Cladosporium trichoides*, 811
- Cladribine, 324
  - during pregnancy, 594
- Clindamycin, 615, 620, 620*t*, 824, 827
- Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar), 629
- Clobazam, 321, 1009*t*, 1010*t*
- Clofazimine, for leprosy, 735–736, 738
- Clofibrate, 616, 624
- Clonazepam
  - for parasomnias, 934*t*
  - for REM sleep behavior disorder, 1109
  - for restless legs syndrome, 932*t*
  - for sleep-related eating disorders, 934*t*
- Clonidine, 221, 225
- Clopidogrel, for stroke risk reduction, 114, 975
- Clotting factor deficiencies, 461
- Clozapine, 605*t*, 606, 611–612, 1014*t*, 1021, 1028, 1036*t*, 1045
- Cluster breathing, 10
- Coagulation disorders, 468–474
  - antiphospholipid antibodies. *See* Antiphospholipid antibodies (aPL)
  - in cancer, 181
    - and stroke, 181
  - factor VIII, 473
  - hereditary thrombophilia
    - antithrombin III deficiency, 471
    - arterial thrombosis and, 473–474
    - description of, 471–472
    - factor V Leiden, 473
    - interactions between, 473
    - protein C deficiency. *See* Protein C, deficiency of
    - protein S deficiency. *See* Protein S, deficiency of
    - prothrombin G:A 20210 mutation, 472
    - stroke and, 473
  - hyperhomocysteinemia, 172–173, 239, 258, 420, 442, 471, 473
  - patent foramen ovale, 474
- Coagulation system, changes in, 174
- Coagulative myocytolysis, 160
- Coarctation of the aorta, 38–39
  - neurologic sequelae of, 38, 38*t*
  - steal in, 39*f*
  - subarachnoid hemorrhage associated with, 38
  - surgical treatment of, 39–40
  - in Takayasu arteritis, 38
- Coasting, 617, 648, 648*t*, 652, 781, 1073
- Cobalamin. *See* Vitamin B_{12}
- Cocaine
  - administration of, 638
  - chronic use of, 638
  - dyskinesias and, 1028
  - in Horner syndrome diagnosis, 435
  - hyperthermia and, 666*t*
  - movement disorders and, 1039
  - neurologic complications of, 638
  - seizures caused by, 638, 1020
  - and stroke, 185
- Coccidioidal meningitis, 352*t*, 808, 818
- *Coccidioides immitis*, 804*t*, 807–808
- *Coccidioides posadasii*, 807–808
- *Coccidioides* spp., 790
- Coccidioidomycosis
  - diagnosis of, 808, 814
  - meningitis in, 352*t*, 807–808, 818
  - neurocutaneous manifestations of, 352*t*
- Cochlear ototoxicity, drug-induced, 410
- Cockayne syndrome, 359

Codeine, 258, 312, 318, 1014*t*, 1052, 1115
Codeine linctus, 624–625
Coenzyme Q10 deficiency, 366*t*
Cogan lid twitch, 430
Cogan syndrome, 36*t*, 408
Cognitive behavioral therapy (CBT), 946
  for insomnia, 918, 919*t*
Cognitive dysfunction. *See also* Dementia
  diabetes mellitus and, 313–314
  drugs causing, 608–609
  HIV and, 772–773, 1103
  hypertension related, 119
  hypothyroidism and, 1103
  MDMA use and, 640
  obstructive sleep apnea and, 18–19, 1104
  postoperative, 981
  systemic lupus erythematosus and, 888
Cognitive function before and after CABG, 46
Coil embolization, 106
Cold agglutinin disease, 445–446
Cold pressor test, 138
Collapsin response-mediator protein, 513
  CRMP5, 129, 1031, 1060
Collapsing/give-way weakness, 942
Colonic pseudo-obstruction, 225
Color vision disorders, 615
Colorado tick fever virus
  encephalitis caused by, 754–755
  meningitis caused by, 743*t*, 746
Colorectal cancer, 1061
Colostomy, 225
Coma, 9, 45, 433. *See also* Brain death; Hepatic encephalopathy; Minimally conscious state; Persistent vegetative state; Uremic encephalopathy; *individual diseases*
  alcohol and, 627, 631–633
  amebic encephalitis and, 830–831
  bacterial infections of CNS, 693, 697, 700
  barbiturate, 989
  brain death, 1096*t*, 1097–1098, 1097*f*
  causes of, 433
  cerebral malaria and, 823, 829
  chronic meningitis and, 841–845
  clinical approach to, 1092–1095
  definition of, 1086–1088
  drug-induced, 606–607
  eclampsia and, 599
  electrolyte disturbances and, 273–280, 451
  Hashimoto encephalopathy and, 299–300
  hemolytic-uremic syndrome, 466
  hyperthyroidism and, 298–299
  hypoglycemic, 304
  hypothyroidism and, 287–288
  hypoxic-ischemic, 45, 147–155
  intracranial hemorrhage, 109, 110*t*
  intracranial hypertension, 111
  mechanisms of, 1088–1092
  neuroanatomic localization of, 1088*t*
  niacin deficiency and, 246
  nonketotic hyperosmolar, 303–304, 357*t*
  after occupational toxic exposure, 651, 656–657, 659
  pellagra and, 209
  pertussis and, 864
  postoperative, 979–981
  prognosis for, 1095
  recreational drugs and, 638, 640–643
  sleep versus, 1088
  stroke, 45, 117
  subarachnoid hemorrhage and, 107, 107*t*
  temperature abnormalities and, 663*t*, 665, 667, 669–670
  transplants and, 785–786
  tuberculous meningitis, 719, 719*t*, 725
  viral meningitis/encephalitis, 742, 749, 751, 754–756, 761
  and vitamin A toxicity, 246
  Waldenström macroglobulinemia, 451
Comitant misalignment, 424–425
COMMANDER HF trial, 80
Common fibular nerve injury, 596
Communicating hydrocephalus
  in bacterial infections, 690, 691*f*
  in cryptococcal meningitis, 779
  dementia and, 1104
  magnetic resonance imaging of, 1104*f*
  in meningeal leukemia, 447
  in sarcoidosis, 873
  simulating parkinsonism, 1045
  in tuberculous meningitis, 719
Complement-fixing antibodies (CFAs), 808
Compound muscle action potentials (CMAPs), 306, 999, 1003
Compressive neuropathies, prevention of, 49
Compressive optic neuropathy, 421
  due to meningioma, 421*f*
Computed tomography. *See also specific disorders*
  high-speed, 955
  neurologic complications of, 953–955
  for patients with infective endocarditis, 94
  pulmonary function evaluations, 7
  thorax, 7
Computed tomography angiography, 44, 68, 94, 113, 116, 118, 270, 309, 405, 699–700, 953
Computed tomography myelography, 385, 487, 955–958
Computerized tomographic (CT) imaging after cardiac arrest, 153
Concussion/mild traumatic brain injury (mTBI), 673. *See also* Postconcussion syndrome
  active recovery, 678–679
  biomarkers, 674–675
  clinical approach, 675–679
  definitions, 673–674
  diagnosis, 675–676
  epidemiology, 673–674
  management, 677–678, 677*t*
  neurodegenerative disease, subsequent development of, 679, 1045
  pathophysiology, 674–675
  subtypes, 679
Conductive hearing loss, 392–393
Confusion Assessment Method for intensive care unit (CAM-ICU), 988
Confusional arousals, 933
Confusional state, drug-induced, 608
Congenital central hypoventilation syndrome, 9
Congenital heart disease (CHD), children with, 53–60
  brain dysfunction, neurologic manifestations of, 60–62
    acute symptomatic seizures, 60–61
    acute-onset movement disorders, 60
    epilepsy, 61
    neurodevelopmental disability, 61–62
  complex congenital heart disease, 53–60
    acute cerebrovascular complications, 56
    arterial ischemic stroke (AIS), 56–59, 57*t*
    brain development, delayed, 54
    brain malformations, 55

Congenital heart disease (CHD), children with (*Continued*)
    cerebral venous sinus thrombosis, 59
    genetic disorders, 54–55
    hemorrhagic stroke, 59
    septic embolism, 59–60
    “silent” brain injury in the neonate, 55–56
Congenital hypothyroidism, 286
Congenital myasthenia gravis, 598
Congenital myotonic dystrophy, 598
Congenital nystagmus, 432–433
Congenital rubella syndrome, 860
Congenital syphilis, 707
Congenital toxoplasmosis, 590
Congestive heart failure, 75
Connective tissue diseases, 885–890, 1015–1016
Connective tissue disorders
  myopathies in, 897–898
  otoneurologic manifestations of, 408
  rheumatoid arthritis. *See* Rheumatoid arthritis (RA)
  Sjögren syndrome. *See* Sjögren syndrome
  systemic lupus erythematosus. *See* Systemic lupus erythematosus (SLE)
  systemic sclerosis, 893–894
Consciousness. *See also* Coma; Brain death; Minimally conscious state; Persistent vegetative state
  anatomy of, 1086, 1086*t*, 1087*f*
  arousal component of, 1085–1086
  cancer effects on, 1091
  components of, 1085–1086, 1086*t*
  content component of, 1085–1086
  definition of, 1085–1086
  disordered
    brain death, 1096*t*, 1097–1098, 1097*f*
    cerebrospinal fluid studies of, 1094
    clinical approach to, 1092–1095
    computed tomography of, 1093
    diagnosis of, 1094–1095
    electroencephalography of, 1093
    electrophysiologic studies of, 1093–1094
    evoked potential monitoring of, 1094
    laboratory studies, 1094
    lumbar puncture evaluations, 1094
    magnetic resonance imaging of, 1093
    mechanisms of, 1088–1092
    metabolic encephalopathies, 1088, 1089*t*
    neuroimaging of, 1093
    persistent vegetative state, 1097–1098
    prognosis for, 1095
    systemic disorders that cause, 1091–1092
    treatment of, 1094–1095
  historical perspective of, 1085
  minimally conscious state, 1097–1098, 1117
  postoperative impairment of, 981*t*
  systemic diseases and, 1086–1088
Constipation, 222–223
  in multiple sclerosis, 228
  in parkinsonism, 225–226
Contactin-1 antibodies, 517
Continuous positive airway pressure
  for obstructive sleep apnea, 926
Continuous Reaction Time Test (CRT), 195
Continuous renal replacement therapy (CRRT), 1013
Contraction band necrosis, 160
Contrast media
  arachnoiditis and, 958
  gadolinium-based, 952
  intrathecal injections of, 955–958
  iodinated, 951–952
  magnetic resonance imaging, 952–953
  neurologic complications of, 951–953
  nonionic, 957
  reflux of, 953
  seizures and, 958
  venous air embolism during infusion of, 953
  water-soluble, 958
Conventional external beam radiation therapy, 488
Convergence, 427
Conversion disorder. *See* Functional neurologic disorders (FNDs)
Copper. *See also* Wilson disease
  deficiency of, 202, 210, 240–241, 1064*t*, 1072
    clinical manifestations of, 210, 236, 236*t*, 240, 1072
    diagnosis of, 236*t*, 241
    etiology of, 240
    hematologic abnormalities with, 241
    magnetic resonance imaging of, 241, 241*f*
    treatment of, 236*t*, 241
  dystonia caused by accumulation of, 1026
Coproporphyria, 357*t*, 358, 366*t*
Corneal light reflex, 424
Coronary angiography
  after ischemic stroke, 166–167
  for patients with acute stroke, 166–167
  after subarachnoid hemorrhage, 167
Coronary artery bypass grafting (CABG), 43–46, 50–51
  atrial fibrillation after, 44
  cognitive function before and after CABG, 46
  encephalopathy after, 45
  intracerebral hemorrhage after, 44
  ischemic complications following, 44–45
  low cardiac output after, 44
  nonstroke neurologic complications after, 45–46
  postoperative strokes following, 44
  stroke after, 44–45
  symptomatic carotid stenosis in patients undergoing, 51
  valvular heart surgery and, 44
  visual disorders associated with, 44–45
Coronary artery disease (CAD), 159–160, 166–167. *See also* Coronary angiography; Coronary artery bypass grafting (CABG)
  atrial fibrillation and, 69, 71
  cardiac conduction abnormalities and, 83, 133
  carotid atherosclerosis and, 117
  cerebrovascular disease and, 166–167
  folate deficiency and, 239
  and headache, 1049
  hormone replacement therapy and, 320, 325
  and migraine, 183, 185
  myocardial necrosis in, 159–160
  in patients with ischemic stroke, 159–160, 166–167
  sexual activity and, 573
  sleep disorders and, 917*t*, 925
  vascular dementia and, 1100
Coronary microvasculature, catecholamine surge on, 161–162
Coronary subclavian steal syndrome, 30–31
Corpora cavernosa, 560
Corpus callosum agenesis, 663–664
Cortical blindness, 44–45, 121, 148, 356, 523, 526–527, 606, 615
  description of, 615
Cortical myoclonus, 1038
Corticobasal degeneration, 1102, 1105*t*

Corticosteroids, 595, 737–738, 798–799, 898, 1052, 1053*t*
  alternatives to, 882
  for brain abscess, 695
  cervical radiculopathy treated with, 375
  for cranial neuropathy, 880–881
  for HTLV-associated myopathy/tropical spastic paraparesis, 783
  for hydrocephalus, 881
  immunosuppressant use of, 798–799
  myopathies caused by, 623, 798–799, 900, 1077
  neurologic complications of, 798–799
  for neurosarcoidosis, 883
  for nonsystemic vasculitic neuropathy (NSVN), 900
  osteoporosis risks, 883. *See also* Osteoporosis
  for parenchymal disease, 881
  for polymyalgia rheumatica, 903
  for polymyositis, 1080
  psychiatric complications of, 799
  radiation necrosis treated with, 533
  for sarcoidosis, 868, 881
  for schistosomiasis, 837
  for spinal tuberculous arachnoiditis, 724
  for systemic lupus erythematosus, 889–890
  for systemic vasculitis, 902
  for Takayasu arteritis, 904
  for temporal arteritis, 902
  withdrawal from, 799
Corticotropin stimulation test, 339
Corticotropin-releasing hormone, 332
Corynebacterium diphtheriae, 860
Cotton wool spots, 44–45
COVID-19 infection, 760–761
Cowden disease, 362*t*
Coxsackieviruses, 743*t*
Cramps, drug-induced, 624
Cranial epidural abscess. *See also* Epidural abscess
  clinical presentation of, 697
  definition of, 695–696
  diagnosis of, 697
  etiology of, 696
  illustration of, 696*f*
  magnetic resonance imaging of, 697
  treatment of, 697
Cranial myeloma, 449–450
Cranial neuropathy
  in beriberi, 243–244
  cerebral aneurysm and, 106
  corticosteroids for, 881
  hypothyroidism and, 289
  in Lyme disease, 711–712
  in lymphoid granulomatosis, 455
  metastases and, 496
  in neurolymphomatosis, 496
  radiation injury and, 534
  in relapsing polychondritis, 393
  in sarcoidosis, 871–872, 879–881, 883
  skull-base metastases and, 482, 483*t*
  in systemic lupus, erythematosus, 888*t*, 889
  in systemic vasculitis, 900–901
  vincristine neurotoxicity and, 526*t*
Craniopharyngiomas, 329, 330*t*, 337*t*, 421*t*, 432, 567
Craniotomy
  awake, 987
  seizures after, 986
  subdural empyema and, 696
C-reactive peptide (CRP), 898
C-reactive protein (CRP), 70, 92, 694
Credé maneuver, 553–554
CREST syndrome, 893
Creutzfeldt–Jakob disease, 300, 424, 512, 611, 632, 759, 760*f*, 1034–1036, 1044
Critical flicker frequency, 194–195
Critical illness myopathy, 12*t*, 15, 997*t*, 998*t*, 1002–1006, 1004*f*. *See also* Quadriplegic myopathy, acute
  cachectic myopathy and, 1005
  critical illness polyneuropathy (CIP) and, 998–1001
  description of, 1004–1005
  diagnostic criteria for, 1003*t*
  histologic findings in, 1004*f*
  management of, 1004
  rhabdomyolysis versus, 1081–1082
  risk factors for, 1081–1082
  thick-filament myosin loss in, 1004–1005
Critical illness polyneuropathy (CIP), 14, 998–1001
  characteristics of, 998*t*
  critical illness myopathy and, 1002–1004
  description of, 1070–1071
  diagnostic criteria for, 999*t*
  electrodiagnostic studies of, 997, 999
  euglycemia in, 1001
  failure to wean from mechanical ventilation, 998
  histologic features of, 1000*f*
  intravenous immunoglobulin for, 1001
  muscles affected by, 998–999
  risk factors for, 1000–1001
  vascular endothelium in, 1001
Critically ill patients
  acute necrotizing myopathy of intensive care in, 1005
  cachectic myopathy in, 1005
  co-existing critical illness polyneuropathy and myopathy, 1005–1006
  encephalopathy in, 1090
  muscle biopsies in, 997
  neuromuscular conditions in, 996–1006, 998*t*
    chronic polyneuropathies, 1002
    critical illness myopathy. *See* Critical illness myopathy
    critical illness polyneuropathy. *See* Critical illness polyneuropathy (CIP)
    differential diagnosis of, 997*t*
    electrodiagnostic testing of, 997
    motor neuropathy, 1001–1002
    myopathies, 1002
    neuromuscular transmission disorders in, 1002
    overview of, 996
    rhabdomyolysis in, 998*t*, 1005
  rhabdomyolysis, 1005
  seizures in, 1012–1015
    treatment of, 1013–1014
  septic encephalopathy in. *See* Sepsis-associated encephalopathy
  thick-filament myosin loss, 1004–1005
  transient neuromuscular junction blockade in, 1002
Crizotinib, 481, 482*t*, 492
CRMP5 antibody, 505, 510–511
Crohn disease
  aortitis and, 36*t*
  description of, 205–207, 1016
  multiple sclerosis and, 206
  myasthenia gravis and, 207
  myelopathy and, 206
  myopathy and, 206
  pellagra and, 210

Crohn disease (*Continued*)
  restless legs syndrome and, 932t
  seizures and, 206
  small bowel syndrome and, 796–797
  stroke and, 206
  Wernicke encephalopathy and, 207
Cronkhite–Canada gastrointestinal hamartomatous polyposis, 366t
Crush syndrome, 620
Cryoglobulinemia, 446
  and stroke, 178
Cryoglobulinemic neuropathy, 1067
Cryoglobulinemic vasculitic neuropathy, 1065
Cryoglobulins
  definition of, 178
  stroke and, 178–180
Cryptococcal meningitis, 776t, 779, 805–807, 809, 812–817, 842, 1018, 1029t, 1030
Cryptococcosis, 352t
Cryptococcus gatti, 806–807
Cryptococcus neoformans, 779, 787, 804t, 806–807, 1103
Cryptococcus species, 841–843
  diagnostic testing, 842
  presentation, 842
  risk factors, 842
  treatment, 842–843
Cryptogenic stroke, 66–67, 73, 175, 474
CT angiography (CTA), 94
CTLA-4 competitive binding, 460
C-to-T mutation, 473
Cushing disease, 332, 338–339
Cushing reflex, 157–158
Cushing syndrome, 338–339
Cutaneous small-vessel vasculitis, 368f
Cutaneous zoster, 752
Cyanide poisoning, 1025
Cyanotic congenital heart disease, 693
  endothelial injury in, 57
  hemorrhagic stroke in children with, 59
  infective endocarditis with secondary embolism in children with, 59–60
  periprocedural strokes in patients with, 57–58
Cyclophosphamide, 1069
  for systemic lupus erythematosus, 889–890
Cyclophosphamide, 336t, 368, 394, 462, 465, 482t, 506, 506t, 512, 517, 522t, 523t, 597, 763, 798t, 849, 862, 889–890, 893, 899–900, 902, 917, 1037, 1048t, 1066–1067, 1070
Cycloplegia, 614
Cyclosporine, 797, 898, 1069
  clearance of, 1017
  neurologic complications of, 797
  posterior leukoencephalopathy caused by, 606
  posterior reversible encephalopathy caused by, 121
  posterior reversible leukoencephalopathy caused by, 622f
CYP3A4 substrates, 1050
Cyproheptadine, 985
Cystathionine β-synthase deficiency, 348t
Cystic echinococcosis, 833–834
Cystic medial necrosis, 37–38
Cysticercosis, 831–833, 1079
Cystometry, 550, 551f
Cytarabine
  Intrathecal, 492, 530
  neurologic complications of, 121, 512, 522t, 523t, 524–525, 604, 605t, 606, 611–612, 616, 617t, 618, 1039t
Cytochrome P450 enzymes, 462
Cytokine release syndrome (CRS), 459, 529, 799
Cytokines, 690
Cytomegalovirus (CMV), 228, 788, 1059
  cauda equina syndrome caused by, 782
  characteristics of, 743t
  description of, 228
  encephalitis, 776t, 779–780
  fetal infection with, 590
  vasculitis, 1083t
Cytotoxic T-cell receptor, 529
Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), 481, 529, 800

D

Dabigatran, 79, 468, 983
Dabrafenib, 481, 482t, 492
Danazol, 319, 326–327, 604, 619
Dantrolene, 572t, 613, 624, 966, 985
  for malignant hyperthermia, 624, 668, 973, 985
  for neuroleptic malignant syndrome, 985, 1035
Dapsone, 394, 614, 616–618, 734–736
Dapsone resistance, 735–736
DDT. *See* Dichlorodiphenyltrichloroethane (DDT)
De Feo score, 96
Death rattle, 1116
De-efferented state, 1119
Deep brain stimulation (DBS)
  arousal after, 1118
  for dyskinetic reactions, 610
  for dystonia, 6, 10, 1027–1028, 1033
  for essential tremor, 1041
  for Parkinson disease, 567, 966, 987, 1045–1046
  for postural hypotension, 141t, 142t, 144
  for Wilson disease, 214
Deep breathing, and heart rate, 137, 137f
Deep hypothermic circulatory arrest, 62
Deep vein thrombosis (DVT), 67t, 69, 96, 390, 472–473, 738, 759, 887, 1005
Deferasirox, 811
Deferoxamine, 263–264, 614, 620t, 804, 804t, 811
Degenerative disease of the spine
  cervical disc disease/spondylosis, 373–375, 374f, 545, 957, 1058–1059
  description of, 373–374
  lumbar disc disease, 375–376, 376f
Deglutition syncope, 133
Degos malignant atrophic papulosis, 351
Dehydration
  cerebral venous sinus thrombosis and, 700
  delirium tremens and, 629
  delirum and, 968t, 969
  hyperthermia and, 667–668
  hyponatremia and, 1034
  jet lag disorder and, 930
Delayed awakening, 979–981
Delayed brain development in fetuses with complex CHD, 54
Delayed sleep phase disorder, 927–928, 928f
Delayed-onset thrombocytopenia, 463
Delirium, 43, 45–46, 51–52, 967–969, 968t, 1090
  agitation and, 1106–1108
  anesthesia and, 968
  from bath salts, 639–640
  characteristics of, 967–968
  from corticosteroids, 799
  definition of, 1090

  dementia and, 1099–1100, 1103, 1105*t*, 1106–1108
  drug-induced, 523*t*, 608, 799
  at end of life, 1115–1116
  factors associated with, 968*t*
  from gamma hydroxybutyrate, 641
  in hospital setting, 1107
  hyperactive, 967–968
  in hyperparathyroidism, 337
  from hyperthermia, 665, 667
  in hyperthyroidism, 298–299
  hypoactive, 967–968
  in hypocalcemia, 278
  in hypokalemia, 278
  in hyponatremia, 274
  in hypothyroidism, 288
  iatrogenic risks of, 968
  in intensive care unit patients, 988
  and liver disease. *See* Hepatic encephalopathy
  management of, 981
  metabolic encephalopathy and, 1090
  monitoring of, 988
  from organophosphates, 656, 657*t*
  in pancreatic encephalopathy, 200
  in pheochromocytoma, 339–340
  postoperative, 967–968, 968*t*, 980*t*, 981
  postoperative associations with, 45
  in rabies, 756
  in relapsing polychondritis, 393
  rhabdomyolysis and, 1083*t*
  in SIADH, 336*t*
  in systemic lupus erythematosus, 888
  in uremic encephalopathy, 252–253
  in viral encephalitis, 749*t*
  in vitamin B_{12} deficiency, 237
  in Wernicke encephalopathy, 244
Delirium tremens, 336*t*, 357*t*, 628–629, 662*t*, 664, 668
δ-aminolevulinic acid (δ-ALA), 653, 1017
Dematiaceous fungi, 804*t*
Demeclocycline, 335*t*, 336
Dementia. *See also individual disorders*
  advanced, 1119–1120
  alcohol-related, 629
  Alzheimer disease, 1099–1100. *See also* Alzheimer disease
  causes of, 1099–1104, 1100*t*
  Cockayne syndrome, 359
  cognitive dysfunction and, 312
  communicating hydrocephalus and, 1104
  dialysis, 263, 1034
  in elderly, 1099
  end of life care for, 1120
  epidemiology of, 1099
  frontotemporal, 1101–1102, 1102*f*, 1105*t*
  HIV-associated, 768, 768*t*, 769*f*, 775, 1103
  hormone replacement therapy and, 325
  hypertension as risk factor for, 101, 118–119
  incontinence and, 1109–1110
  with Lewy bodies, 424, 545, 969, 1100*t*, 1101, 1105*t*, 1107, 1109
  multiple system atrophy and, 1101
  neurocutaneous manifestations of, 359–362
  parkinsonism and, 1101
  postmenopausal estrogen replacement therapy and, 324–325
  postoperative complications of, 969
  preoperative considerations, 969
  prevalence of, 1099, 1119–1120
  semantic, 1101–1102
  structural lesions and, 1103–1104
  subdural hematoma and, 1103–1104
  synucleinopathies, 1101
  syphilis and, 1103
  systemic complications of
    agitation, 1106–1108
    aspiration, 1104–1106
    delirium, 1106–1108
    depression, 1108
    dysphagia, 1104–1106
    falls, 1108
    gastrointestinal, 1109–1110
    genitourinary, 1109–1110
    mood disorders, 1108
    orthostatic hypotension, 1108–1109
    sleep disorders, 1109
  systemic diseases that cause, 1103–1104
  tauopathies, 1101–1103
    chronic traumatic encephalopathy, 1102–1103
    corticobasal degeneration, 1102, 1105*t*
    definition of, 1101–1103
    frontotemporal dementia, 1101–1102, 1102*f*, 1105*t*
    progressive supranuclear palsy, 1102, 1105*t*, 1108
  urinary incontinence and, 545, 1109–1110
  vascular, 313–314, 1100–1101, 1105*t*
  vitamin B_{12} deficiency and, 1103
Demyelinating disorders. *See individual disorders*
Demyelinating optic neuritis, 417
Demyelinating sensorimotor polyneuropathy, 618
Dengue, 864, 1030, 1040, 1043
Dengue shock syndrome, 864
Dengue virus, 744*t*, 755, 763*t*, 864
Denusumab, 384
5-Deoxyadensoylcobalamin, 236–237
Depression
  dementia and, 1100*t*, 1108
  drug-induced, 528–529, 608, 641
  hepatic encephalopathy and, 192
  hyperthyroidism and, 299
  hypothyroidism and, 288
  insomnia and, 917
  in limbic encephalitis, 507
  screening for, 1104
  in Whipple disease, 207, 207*t*
  in Wilson disease, 212
Dermatomyositis, 369, 369*f*, 500–501, 506*t*, 519, 621–622, 897, 1079–1080
Descartes, 1085
Desire stage, of sexual response, 558
Desmopressin, 141, 144, 311, 335, 336*t*, 461, 554
Detrusor areflexia, 546–547
Detrusor overactivity, 544*t*, 545, 549–550, 551*f*, 553
  incontinence associated with, 553
  intravesical pressure affected by, 552–553
  in multiple sclerosis, 546
Detrusor pressure, 549–550
Deutetrabenazine, 610, 1024, 1031, 1033
Dexamethasone, 724, 1052. *See also* Corticosteroids
  for bacterial meningitis, 690–692
  for epidural spinal cord compression, 488
  prophylactic uses of, 530
  for spinal tuberculous arachnoiditis, 724
  for vasogenic edema, 479
Dexmedetomidine, 987–988
Dextroamphetamine (Dexedrine), 611, 922, 922*t*
Dextromethorphan, 315, 613, 643–644
Diabetes and GAD65 antibodies, 1016

- Diabetes insipidus, 276, 334–335, 335*t*, 508, 873–874
- Diabetes mellitus
  - autonomic neuropathy and, 311–312, 972
  - central nervous system complications of
    - Alzheimer disease, 312
    - cerebral infarction and vascular dementia, 313–314
    - cognitive dysfunction, 312–313
    - vascular dementia, 313–314
  - cerebral infarction and, 313–314
  - delayed gastric emptying in, 221
  - dysautonomia in, 128
  - erectile dysfunction in, 311–312, 570
  - gut dysmotility and, 229
  - hearing loss and, 408
  - hyperglycemia and hypoglycemia, neurologic features of, 303
  - hypoglycemia and, 304
  - hypothermia in, 663
  - lacunar infarcts and, 111–114
  - neurocutaneous manifestations of, 348*t*, 362*t*
  - neurodegeneration caused by, 312
  - neurologic features of
    - autonomic neuropathy, 311–312
    - Bell palsy, 310–311
    - bladder neuropathy, 312
    - carpal tunnel syndrome, 308–309. *See also* Carpal tunnel syndrome
    - diabetic ketoacidosis, 303
    - focal mononeuropathies, 308–309
    - gastrointestinal neuropathy, 311
    - intercostal neuropathies, 309–310
    - lumbosacral plexopathy, 310
    - meralgia paresthetica, 309, 595–596
    - oculomotor neuropathy, 310
    - peripheral neuropathies, 304, 1064–1065
    - polyneuropathy. *See* Diabetic polyneuropathy
    - sudomotor neuropathy, 312
    - truncal radicular neuropathies, 309–310
    - ulnar neuropathy at the elbow, 309
  - neuropathic pain and, 314–315
  - nonketotic hyperosmolar syndrome, 304
  - sexual dysfunction in, 311–312
  - and stroke, 172–173
- Diabetic ketoacidosis, 303
- Diabetic leukoencephalopathy, 313–314, 313*f*
- Diabetic lumbosacral plexopathy, 310
- Diabetic microangiopathy, 308
- Diabetic neuropathy, postural hypotension in, 128
- Diabetic papillopathy, 420*t*
- Diabetic polyneuropathy
  - description of, 304
  - differential diagnosis of, 306*t*, 308
  - distal motor wasting in, 305
  - electrophysiologic testing for, 306
  - grading of, 305–306
  - laboratory testing for, 306, 307*f*
  - large-fiber, 305
  - lower urinary tract symptoms in, 546–547
  - motor axon loss in, 306–307
  - nerve conduction abnormalities in, 307*f*
  - neurologic examination in, 304–308
  - pathogenesis of, 308
  - quantitative sensory testing for, 307
  - sexual dysfunction in, 570–571
  - small-fiber, 305
  - “stocking and glove” sensory changes in, 304, 305*f*
  - sural nerve biopsy and, 307
  - symptoms of, 304
  - treatment of, 308
  - weakness in, 304
- Diabetic thoracoabdominal radiculopathy, 1059
- Dialysis
  - cognitive alterations associated with, 260
  - muscle cramps and, 260
  - neurologic complications of, 259–260
    - carpal tunnel syndrome, 261
    - cerebrovascular disease, 260–261
    - dementia, 263, 1034
    - encephalopathy, 1008
    - entrapment mononeuropathies, 261
    - ischemic neuropathy, 261–262
    - osmotic demyelination syndrome, 261
    - subdural hematoma, 260–264
    - ulnar nerve lesions, 261
    - Wernicke encephalopathy, 262–263
  - sleep disturbances caused by, 261
- Dialysis disequilibrium syndrome, 253, 260, 1008
  - headache in, 1051
- Dialysis headache, 1051
  - preventing, 1051
- 3,4-Diaminopyridine, 432, 506*t*, 518, 1076
- Diamorphine, 1036, 1115–1116
- Diaphragm
  - activation of, 6
  - isolated tremor of, 10
  - myoclonus of, 10
  - weakness of, 7
    - alveolar hypoventilation caused by, 15
- Diaphragma sellae, 328
- Diaphragmatic flutter. *See* Diaphragm myoclonus
- Diazepam, for delirium tremens, 628
- Dichloroacetate, 617*t*, 619
- Dichlorodiphenyltrichloroethane (DDT), 658, 1036*t*
- 2,4-Dichlorophenoxyacetic acid (2,4-D), 659
- Dietary Approaches to Stop Hypertension (DASH) eating plan, 103
- Diethylenetriamine penta-acetic acid (DTPA), 952
- Diffuse idiopathic skeletal hyperostosis, 391–392
- Diffuse Lewy body disease, 127. *See also* Dementia, with Lewy bodies; Lewy Body disease
- DiGeorge syndrome, hypoparathyroidism caused by, 338
- Dihydroergotamine, for postural hypotension, 144
- Dihydrofolate reductase, 239
- L-Dihydroxyphenylserine, 141, 142*t*, 143, 311
- Dilated cardiomyopathy, 75, 179*t*, 380, 447, 773
- Dimercaprol, 1035–1037
- Dimethyl fumarate, 324
  - during pregnancy, 593
- Diphtheria, 14, 366*t*, 860, 997, 1029*t*, 1064*t*, 1065*t*
- Diplopia
  - in botulism, 1074–1075
  - in compressive optic neuropathy, 421
  - description of, 424
  - drug-induced, 615
  - in eclampsia, 599
  - in giant cell arteritis, 420–421
  - intranuclear ophthalmoplegia (INO), 429
  - mechanical causes of, 430–431
  - in myasthenia gravis, 430, 1076
  - in oculomotor (III) nerve palsy, 428
  - in paraneoplastic cerebellar degeneration, 509
  - in pituitary apoplexy, 333
  - in septic cavernous thrombosis, 700

  supranuclear causes, 427
  in thyroid-associated ophthalmopathy, 297
  in trochlear nerve (IV) palsy, 428
Discitis, 98, 958–959
Discography, 958–959
Disease-Specific Graded Prognostic Assessment (DS-GPA), 478–479
Disequilibrium of aging, 412, 412*f*
Dissecting aortic aneurysms, 37–38, 40*t*
Disseminated intravascular coagulation, 59, 93, 177, 181, 199, 448, 668–669, 671, 793, 824, 1035, 1092
  description of, 463–465, 464*t*
  in pregnancy, 586
Distal axonal neuropathy, 649
Distal sensory polyneuropathy
  in HIV-infected patients, 781
  treatment of, 781
Disturbed nocturnal sleep
  in narcolepsy, 921
Disulfiram, 608, 619, 1026
  optic neuropathy and, 614
  parkinsonism caused by, 1042
  peripheral neuropathy and, 617*t*, 619, 1064*t*
Disuse myopathy, 998*t*
Diuretic
  hyperthermia and, 666*t*
  postural hypotension and, 125
Divalproex, 1050–1053, 1053*tt*
Divergence, 427
Dix–Hallpike maneuver, 401, 402*f*, 432
Dizziness, 81
  functional, 943–944
  for hypertension, 103–105
  migraine-related, 402–404
DNA vaccines, 855
DNA-damaging drugs
  alkylating agents, 526
  ifosfamide, 243*t*, 336*t*, 522*t*, 523*t*, 526, 606, 1036*t*, 1039*t*
Docetaxel, 121, 506*t*, 522*t*, 523, 523*t*, 606, 1070
Doll's eyes maneuver, 1093
Domperidone, 226, 311, 605*t*, 612*t*, 966, 1026, 1027*t*
Donepezil, 225, 612*t*, 1100–1101
Dopamine
  agonists of, 125, 221, 226, 257–258, 331–333, 334*t*, 567, 572*t*, 610, 613, 670, 931, 966, 985, 1026, 1029*t*, 1035, 1041, 1045–1046, 1109
  sleep and, 914
Dopamine 2 receptor (D2R) antibodies, 508–509
Dopamine *β*-hydroxylase deficiency, 143
Dopaminergic agents, 221
  for periodic limb movements, 931
  for restless legs syndrome, 931
Doppler ultrasound, 30, 68–69, 108, 116, 118, 178, 459, 733, 1097, 1097*f*
Doppler velocimetry, 732
Dorsal respiratory group (DRG), 4, 5*f*
Dorsal rhizotomy, 223
Dorsal root ganglion
  disorders of, 517, 1060–1061, 1060*t*
  latent infection of, 1060–1061
Down syndrome, 325, 925
Doxepin, for insomnia, 920
Doxycycline, 208–209, 615, 687–688, 707, 824
  for Lyme disease, 406, 713–714, 714*t*, 845
Dravet syndrome, 861, 1012
DRESS syndrome, 735
Dropped head syndrome, 528, 534
Drug abuse. *See* Recreational drugs
Drug-induced disorders. *See also* Chemotherapy; Corticosteroids; Recreational drugs; *and individual disorders*
  acute dystonic-dyskinetic reactions, 609
  acute quadriplegic myopathy, 623–624
  acute rhabdomyolysis, 622
  akathisia, 609
  antimicrobial agents, 618
  antineoplastic drugs, 617–618
  antirheumatic drugs, 618
  aseptic meningitis, 604–605
  autonomic disorders, 616–619
  autophagic myopathies, 624
  behavioral toxicity, 607
  bladder dysfunction, 616
  cardiovascular drugs, 618
  cerebellar syndromes, 612
  cholesterol-lowering agents, 618–621
  chorea, 610–611, 1026–1028, 1029*t*
  cognitive impairment, 608–609
  color vision, 615
  coma, 606–609
  confusional state, 608
  cortical blindness, 523, 526–527, 606, 615
  delirium, 608
  diplopia, 615
  drug-induced myopathies, 624–625
  dyskinetic reactions, 609–610
  dystonia, 609–610, 1026–1028, 1029*t*
  encephalopathy, 606
  glucocorticoid myopathy, 623
  hallucinatory states, 608
  headache, 604, 970
  hyperthermia, 666*t*
  hypnotic and psychotropic drugs, 619
  hypothermia, 667*t*
  idiopathic intracranial hypertension, 604
  immune thrombocytopenia, 462
  inflammatory myopathies, 621–622
  levodopa, 619
  levodopa-induced dyskinesias, 610
  malignant hyperthermia, 624
  mitochondrial myopathies, 622–623
  mood disorders, 608
  movement disorders, 609–612
  muscle disorders, 620–625, 621*t*
  myalgia, cramps, and twitches, 624
  mydriasis, 436
  myoclonus, 611, 1034–1037, 1036*t*
  myopathy. *See* Myopathy, drug-induced
  myotonia, 624
  neuroleptic malignant syndrome, 612–613, 662*t*, 664, 666*t*, 985, 1034–1035
  neuromuscular transmission disorders, 619–620
  neuropathy, 450, 1073
  neuropsychiatric, 607–609
  nystagmus, 615
  optic neuropathy, 614–615
  otoneurologic manifestations of, 410–411
  ototoxicity, 410–411, 613–614
  parkinsonism, 611–612, 612*t*, 1041–1046
  peripheral neuropathies, 450, 616–619, 1073
  platelet disorders, 463
  postural hypotension, 125, 616

- Drug-induced disorders (*Continued*)
  - potassium-related myopathies, 623
  - psychoses, 608
  - pupillary changes, 614
  - refractive changes, 614
  - retinopathy, 614
  - seizures, 605–606, 605*t*, 612*t*
  - serotonin syndrome, 613
  - sexual dysfunction, 571–572, 572*t*, 616
  - smell disorders, 615
  - spinal cord compression, 616–619
  - spinal disorders, 616–619
  - stroke, 604–605
  - subarachnoid hemorrhage, 604–605
  - tardive dyskinesia, 609–610, 1027
  - taste disorders, 615
  - tics, 611
  - tremor, 611, 1039*t*, 1040
  - vascular headache, 604
  - visual disorders, 614–615
- Drugs and stroke, 183
  - alcohol, 184, 184*f*
  - amphetamines, 184–185
  - anabolic androgenic steroids, 183–184
  - cannabis and cannabinoids, 185
  - cocaine, 185
  - estrogens, 183
  - migraine medications, 185
  - tobacco, 184
- Dry beriberi, 244. *See also* Beriberi, thiamine deficiency and
- Duane type 1 retraction syndrome, 429
- Duchenne muscular dystrophy
  - cardiomyopathy and, 74
  - gastroparesis and, 231
  - malignant hyperthermia and, 624
  - preoperative considerations for, 624, 972–973
  - respiratory dysfunction associated with, 15
- Duloxetine, 315, 572*t*, 1026
- Dural arteriovenous fistulas (DAVFs), 961
  - in pregnancy, 587–588, 588*f*
- Dural metastases, 483–484, 485*f*
- Dural venous sinus, thrombosis of, 399–400, 400*f*
- Dying-back neuropathy, 649, 1060
- Dysarthria
  - in central pontine myelinolysis, 632
  - cerebellar ataxia and, 289, 362*t*, 508–509, 1041
  - from cytarabine, 524
  - gluten ataxia and, 212
  - hepatic encephalopathy and, 191, 195*f*
  - hypercalcemia and, 279
  - in hypothermia, 669
  - lacunar syndromes and, 113
  - malignant osteopetrosis and, 382
  - from manganese, 655
  - myasthenia gravis and, 430
  - pancreatic encephalopathy and, 199–200
  - in radiation therapy, 532
  - uremic encephalopathy and, 252, 1045
  - vitamin E deficiency and, 208
  - Wernicke encephalopathy and, 244
  - in Wilson disease, 212
- Dysautonomia, 123–145. *See also* Autonomic neuropathy; Autonomic system degeneration; Postural hypotension; *individual disorders*
  - anemia in, 144
  - anesthesia considerations, 145
  - body fluid regulation disturbances associated with, 142, 143*f*
  - cholinergic, 518
  - in diabetes mellitus, 128
  - erectile dysfunction and, 132
  - evaluation of, 133–140
  - fluid deprivation in, 143*f*
  - flushing and, 340
  - management of, 140–145
  - in multiple system atrophy, 130, 988
  - postural hypotension in, 123–145
  - in pure autonomic failure, 129–130
  - selective dysautonomias
    - and gut dysmotility, 227
  - symptoms of, 132–133
    - syncope, 132
      - cardiac syncope, 133
      - hyperventilation, 133
      - neurally mediated syncope, 133
      - postural hypotension, 132
- Dyskeratosis congenita, 362*t*
- Dyskinesias, levodopa-induced, 610
- Dyskinetic reactions, 609–612
- Dysphagia, 219–221, 1104–1106
  - in botulism, 1074–1075
  - in cerebellar ataxia, 509
  - in Chiari malformation, 405
  - in dementia, 1104–1106, 1105*t*
  - in dermatomyositis, 1079–1080
  - at the end of life, 1115–1116
  - in inclusion-body myositis, 1080–1081
  - in myasthenia gravis, 430
  - in parkinsonism, 225–226
  - in pellagra, 210
  - in polymyositis, 1079–1080
  - postpolio, 227
  - in sarcoidosis, 872
  - in scleroderma, 893
  - from spinal cord injury, 226–227
  - from stroke, 225
  - from vincristine neuropathy, 526*t*
  - in Wilson disease, 212
- Dystonia, 12, 1023–1033
  - celiac disease and, 1031
  - characteristics of, 1024
  - childhood-onset, 1032
  - copper accumulation and, 1026
  - diagnosis of, 1032
  - drug-induced, 609–610, 1026–1028, 1029*t*
  - electrolyte disturbances and, 1031
  - functional, 942*t*, 943
  - hypoxemic-ischemic disorders and, 1024
  - magnetic resonance imaging of, 1032
  - paraneoplastic syndromes and, 1031
  - in pregnancy, 592
  - tardive, 610, 1027–1028
  - toxins and, 1025–1026
  - treatment of, 1032–1033
  - tuberculous meningitis and, 1028
- Dystonia gravidarum, 592
- Dystroglycan complexes, 729
- Dystrophin-related protein 2 (DRP2), 729

E

- East African trypanosomiasis, 828
- Eastern equine encephalitis virus, 687, 743*t*, 754–755

Echinococcosis, 833–834, 833*f*
Echinococcus spp., 833*f*
  E. granulosus, 833
  E. multilocularis, 833
Echocardiography, 47, 59, 67, 76–77, 80, 82*t*, 84, 118, 141, 160, 162, 164, 166–167, 393, 972, 975
  for atrial fibrillation, 71–72
  and embolic stroke, 68–69, 73
  for infective endocarditis, 92, 95
  for nonbacterial thrombotic endocarditis, 77, 181–182
Echoviruses, 743*t*
Eclampsia, 416*t*, 599–600, 600*f*
  and disseminated intravascular coagulation, 464*t*, 465
  hypertension associated with, 121
  hypertensive encephalopathy in, 119, 120*f*
  stroke and, 583, 585–586
Ecstasy. *See* MDMA (ecstasy)
Eculizumab, 445
Edinger–Westphal nuclei, 433–434
Edrophonium (Tensilon) test, 14–15, 430, 1075–1076
Efavirenz, 771*t*, 774
Eflornithine, 829
Ehlers–Danlos syndrome type 4, 105
Eighth nerve lesions, manifestataions of, 401
Ejaculation
  aortic disease/surgery, 35, 35*t*
  diabetes and, 311
  disorders of, with neurologic disease, 565–572, 574–575
  drug effects on, 572*t*
  evaluation of, 563
  physiology of, 34, 560–562
  spinal cord injury effects on, 569
  vibration-induced, 569, 574
Elbow, ulnar neuropathy at, 309
Elderly
  delirium in, 968, 968*t*, 981. *See also* Delirium
  dementia in, 1099. *See also* Dementia
  headaches in, 1054
  iatrogenic postural hypotension in, 129
  myxedema coma in, 287
  syncope in, 81, 127
  vitamin B_{12} deficiency in, 237
Electrical syncytium, 218–219
Electrocardiographic abnormalities with acute stroke, 163–164
  Q waves and U waves, 164, 164*f*
  QT prolongation, 163–164, 164*f*
  repolarization abnormalities, 164
Electrocardiographic monitoring for atrial fibrillation, 69
Electroencephalography, 49, 58–59, 149–151, 686. *See also individual diseases*
  after cardiac arrest, 151–152, 154
  Creutzfeldt–Jakob disease, 759–760
  disordered consciousness, 1093
  in drug-induced coma, 607
  in hepatic encephalopathy, 193–196, 195*f*
  in herpes simplex virus encephalitis, 686
  in hyperthermia, 667
  in hypothermia, 669
  in hypothyroidism, 287
  ifosfamide and, 526
  methotrexate and, 523–524
  myoclonus and, 151
  nonconvulsive status epilepticus, 1014–1015
  occupational neurotoxin exposure, 650
  in paraneoplastic syndromes, 507
  reactivity in, 152
  for seizures, 968–969
  septic encephalopathy, 995, 996*f*
  sleep, 912, 913*f*, 1088
  sleep disorders, 915
  in uremic encephalopathy, 252–254, 255*f*
Electrolyte disturbances
  calcium, 278–279
  encephalopathy and, 1090
  hypothermia and, 670
  magnesium, 279–280
  potassium, 277–278
  sodium, 273–276
Electromyography. *See also individual diseases*
  concentric needle, 551
  lower urinary tract dysfunction evaluations, 551–552
  myopathies, 897
  in neurosarcoidosis, 878
  occupational neurotoxin exposure, 650
  pelvic floor, 551
  polymyositis, 1080
  sleep disorders, 915
  sphincter, 551–552
Electrophysiologic tests, for cardiac arrest prognostication, 151–152
Eletriptan, 1050, 1052
Embolic shower, 980
Embolic stroke. *See* Cardioembolic stroke
Embolic strokes of undetermined source (ESUS), 66–67
Embolism
  amniotic fluid, 584
  cardiogenic brain embolism. *See* Cardioembolic stroke
  infective endocarditis neurologic complications caused by, 88, 89*f*, 91*t*
  septic
    in children with congenital heart disease, 59–60
    hemorrhagic stroke, 88
    intracerebral hemorrhage caused by, 88
    magnetic resonance imaging of, 89*f*
Embolization procedures, neurologic complications of, 961–962
Emergency reperfusion treatment, 77–78
  endovascular therapy, 78
  thrombolysis, 58, 77
Emery–Dreifuss muscular dystrophy, 74, 972
Emetine, 621*t*, 624–625
Empty sella, 329
Encephalitis, 97, 791–792, 800. *See also* Meningoencephalitis; Viral encephalitis; *specific organisms*
  amebic, 830
  anti-NMDA receptor, 460, 502, 761
  approach to viral, 758–759
  arthropod-borne virus, 687
  and ataxia, 362*t*
  basal ganglia, 508–509
  brainstem, 433, 508–509
  after CABG, 45
  CD8 T-cell, 772
  cytomegalovirus, 776*t*, 779–780
  dengue, 864
  enterovirus, 746
  herpes simplex, 686, 742, 750–751, 750*f*
  human immunodeficiency virus, 772–773, 1018
  and hyperthermia, 662*t*
  LCMV, 742
  limbic, 274, 393–394, 460, 501*t*, 506*t*, 507–508, 1015
  Lyme disease, 711, 712*t*

Encephalitis (*Continued*)
  Rabies, 755–756
  SIADH, 336*t*
  signs and symptoms, 749*t*
  skin manifestations, 352*t*
  specific agents, 743*t*
  Toxoplasma, 826
  treatment of, 751*t*
  varicella zoster, 742, 751–753
  viral, 748–759. *See also* Viral encephalitis
  voltage-gated potassium channel, 274
  West Nile virus, 753–754
Encephalomyelitis, 508
  acute disseminated, 761, 762*f*, 855
  experimental allergic, 761–762
  postinfectious, 761–762, 762*f*, 763*t*
Encephalopathy, 51–52, 460, 651. *See also specific causes and disorders*
  acute, 530, 648
  after CABG surgery, 45
  in antiphospholipid syndrome, 470–471
  bovine spongiform, 759
  brainstem, 531–532
  after cardiac transplant, 51–52
  after cardiac valve replacement, 50
  chemotherapeutic agents and, 523*t*
  chimeric antigen receptor T-cell (CAR-T) therapy and, 459, 529, 606
  chronic traumatic, 679, 1102–1103
  cisplatin and, 527
  congenital hypothyroidism and, 286
  COVID-19 infection and, 760–761
  in critically ill patients, 1090
  cytokine release syndrome, 529
  dialysis, 253, 261, 263, 1008
  drugs that cause, 523*t*, 606
  early delayed, 532
  electrolyte disturbances and, 1090
  Hashimoto, 299–301, 1016, 1035–1037, 1041
  hepatic. *See* Hepatic encephalopathy
  human immunodeficiency virus and, 359, 589
  hypercapnic, 18
  hypertensive, 101–102, 119–121, 120*f*
    calcineurin inhibitors and, 797
    causes of, 101, 119
    diagnostic imaging of, 119–121
    signs and symptoms of, 119
    treatment of, 121
    vasogenic cerebral edema and, 119–121
  hyperthyroidism and, 298
  hypoglycemic, 1089
  hyponatremic, 274, 335, 1019
  hypothyroidism and, 287–288
  hypoxic-ischemic, 18, 49, 147–148, 151, 153, 1089, 1094–1095, 1098
  infective endocarditis and, 98
  intermittent, with skin manifestations, 357, 357*t*
  lead, 653
  Lyme, 711
  lymphomatoid granulomatosis, 455
  macrophage activation syndrome and, 459
  metabolic, 10, 793–794, 1088–1090, 1089*t*, 1094
  methotrexate toxicity, 530*t*
  methyl *n*-butyl ketone, 652
  mitochondrial, 408
  myoclonic, 606
  niacin deficiency and, 246
  occupational neurotoxin exposure and, 648–649, 651
  after organ transplantation, 785–786
  pancreatic, 199–200
  pertussis, 861
  posterior reversible (PRES), 121, 253, 254*f*, 259–261, 279, 416*t*, 466, 528, 599, 600*f*, 615, 787*f*
  in post-transplantation period, 785–786
  presenting as persistent coma, 45
  radiation therapy and, 530–532
  septic. *See* Sepsis-associated encephalopathy
  in systemic lupus erythematosus, 356
  toxic, 298, 650–651, 655, 862, 980, 981*t*. *See also specific toxins*
  uremic. *See* Uremic encephalopathy
  vitamin B_{12} deficiency and, 443–444
  Wernicke. *See* Wernicke encephalopathy
Encephalopathy-vasculopathy, in sarcoidosis, 874–875, 874*f*
End of life care
  advance directives, 1113–1114, 1114*f*
  in advanced dementia, 1119–1120
  amyotrophic lateral sclerosis, 1120–1122
  autonomy of patient, 1112
  cardiopulmonary resuscitation, 1114–1115
  de-efferented state, 1119
  functional imaging of, 1119
  hydration and, 1116
  minimally conscious state, 1117–1119
  nutrition and, 1116
  pain during, 1112, 1115
  palliative care and, 1117
  patient–proxy relationship, 1113–1114
  persistent vegetative state, 1085–1086, 1117–1119
  physician–patient interactions, 1111–1115
  provision of, 1115–1117
  quality of life considerations, 1115
  refusal of medical treatment, 1112–1113
  surrogates, 1113
  ventilator support withdrawal in, 1116
  zolpidem and, 1118–1119
Endarterectomy
  carotid, 51, 116–117, 116*t*, 259, 962, 974, 976
  encephalopathy following, 119
Endarteritis obliterans, 706
Endocarditis, 76–77. *See also* Infective endocarditis (IE)
  bacterial, 179
  brain abscess and, 694, 695*t*
  intravenous drug abuse and, 645
  Libman–Sacks, 180–181
  marantic. *See* Nonbacterial thrombotic
  neurocutaneous manifestations of, 348*t*, 351
  nonbacterial thrombotic, 77, 181–182, 181*f*, 793, 1091–1092
  stroke and, 645
Endocrine disorders. *See also specific disorders*
  hearing loss and, 408
  otoneurologic manifestations of, 408–409
  postural hypotension caused by, 125
  and seizures, 1019–1020
Endolymphatic sac tumors, 411–412, 412*f*
Endomyocardial fibrosis, 74–75
Endoneurial granulomas, 875–876
Endoneurial vessels in the armadillo, 727
Endoneurium, 870
Endothelial cells, 91*t*, 115–116, 121, 175, 177*f*, 307, 327, 351, 356, 471–472, 589, 690, 691*f*, 748–749, 823, 894, 994, 1001, 1067, 1080
Endothelin, 161–162

Endovascular therapy
  of aneurysms, 97, 107, 168, 961
  of arteriovenous malformations, 961
  for atrial fibrillation, 78
  for carotid stenosis, 117
  for intramedullary arteriovenous malformations, 962
  in stroke, 95–96, 166–167
  for vertebrobasilar insufficiency, 405
End-stage renal disease (ESRD), 258
  headache in, 1051–1052
Enolase, 153
Entamoeba histolytica, 831
  cerebral amebiasis caused by, 831
  characteristics of, 822*t*
Enteral tube feeding, 1106
Enteric and extrinsic nervous supply to the digestive tract, 218–219
Enteric nervous system, 218–219
Enteric plexuses, 218, 219*f*, 221, 228
Enterococci, 91
Enteroviruses, 864
  characteristics of, 743*t*
  definition of, 742–746
  encephalitis caused by, 756
  meningitis caused by, 742–746
  polioviruses, 742
Entrainment test, 942
Entrapment neuropathy
  carpal tunnel syndrome. *See* Carpal tunnel syndrome
  description of, 1064
  dialysis and, 261
  digital blood flow in, 138
  in hypothyroidism, 291
  meralgia paresthetica, 309, 595–596
  in pregnancy, 596
Environmental disorders, 411
Enzyme-linked immunoelectrotransfer blot (EITB), 832
Eosinophilic granulomatosis with polyangiitis (EGPA), 901
Eosinophilic meningitis, 458*t*, 822*t*, 834–835, 837
Eosinophilic myositis, 457
  and fasciitis, 622
Eosinophilic pleocytosis of CSF, 812
Eosinophilic syndromes, 457–458, 458*t*
Epiaortic ultrasound, 47
Epidermal growth factors (EGFR) tyrosine kinase inhibitors, 492
Epidermoid tumors, 956
Epidural abscess, 983, 983*t*
  cranial, 695–697
  spinal, 697–699
Epidural anesthesia
  complications of, 982
  Horner syndrome after, 985
  neural block, 959
Epidural blood patch, 956, 970, 986
Epidural hematoma
  acute, 957
  anesthesia-related, 982
  postoperative, 982
Epidural lipomatosis, 332, 799
Epidural spinal cord compression
  clinical features of, 486
  diagnostic studies of, 486–487
  epidemiology of, 485–486
  pathophysiology of, 486
  prognosis for, 489
  treatment of, 488–489
Epilepsy, 16
  anesthesia, general in, 970–971, 988
  antiphospholipid syndrome and, 470
  autoimmune diseases and, 1015–1016
  cardiac disease and, 1011
  cardiac manifestations of, 165–166
  catamenial, 321
  celiac disease and, 204
  in children, 987–988
  and congenital heart disease, 61
  connective tissue diseases and cerebral vasculitis, 1015–1016
  diabetes and GAD65 antibodies, 1016
  gestational, 321
  Hashimoto encephalopathy and, 1016
  inflammatory bowel disease, 1016
  interictal phenomena, 566
  limbic encephalitis, 1015
  maternal
    bleeding disorders and, 579–580
    breast-feeding, 580
    fetal effects of, 579
    fetal malformations and, 579
    management of, 580–581
    obstetric management of, 580–581
    seizures in, 578–579
    withdrawal symptoms, 580
  multiple sclerosis and, 1016
  obstructive sleep apnea in, 19, 936–937
  parasomnias versus, 937
  in perioperative period, 970–971
  sex hormones and, 320–321
  sexual dysfunction and, 566
  sleep disorders in, 936
  sudden unexpected death in, 165–166
  in systemic lupus erythematosus, 1015
  thyroid disease and, 1016
Epileptic seizures (ESs), 943, 985–986. *See also* Seizures
Epileptogenesis, 321, 1022
Epineurial granulomas, 875–876
Epithelial cell adhesion molecule (EpCAM), 491
ε-aminocaproic acid, 624–625
Epstein–Barr virus (EBV), 179*t*, 228, 265–266, 453, 756–757, 763*t*, 778, 788*t*, 847, 850, 1029*t*, 1059, 1060*t*, 1069, 1079, 1083*t*
Epworth Sleepiness Scale, 915, 936, 1109
Erectile dysfunction. *See also* Sexual dysfunction
  after aortic disease/surgery, 35, 35*t*
  Arnold–Chiari malformation and, 570
  in diabetes mellitus, 311–312, 570
  in multiple sclerosis, 568
  multiple system atrophy and, 567
  pelvic fracture and, 570
  sclerosing agents and, 570
  after stroke, 565
  vasogenic, 564
Ergot alkaloid derivatives, for migraine, 185
Ergotamine, 614
Ergot-containing preparations, 581
Ergots, 1050, 1052, 1053*t*
Erlotinib, 481, 492, 523*t*
Erythema chronicum migrans, 707–708
Erythema infectiosum, 756
Erythema migrans, 709–710
Erythema nodosum leprosum (ENL), 736–738
  management of, 738
Erythrocytosis, 455–456

- Erythromycin, hypothermia and, 667*t*
- Erythropoietin, 119, 141*t*, 142*t*, 144, 455–456, 523*t*, 605–606, 605*t*, 882
- E-selectin, 1001
- Eslicarbazepine, 1010*t*
- Esophageal dysphagia, 219
- Essential mixed cryoglobulinemia, 1067
- Essential thrombocythemia, 457
- Essential tremor in pregnancy, 592
- Estrogen
  - Alzheimer disease and, 324–325
  - chorea and, 321–322, 1027*t*
  - depression and, 326
  - epilepsy and, 321, 578
  - gliomas and, 323
  - intracranial hypertension and, 327, 604
  - meningiomas and, 323
  - migraine and, 318–319, 581, 1048*t*
  - neuromuscular disorders and, 327
  - parkinsonism and, 322
  - periodic paralysis and, 294
  - premenstrual syndrome and, 326
  - sexual function and, 560, 563, 575
  - sleep and, 326–327
  - and stroke, 183, 583, 586, 604–605
  - Wilson disease and, 213, 322–323
- Estrogen receptor-α, 326
- Eszopiclone for insomnia, 641, 919
- Ethambutol, 416*t*, 614–615, 618, 723–724, 780
- Ethical issues. *See also* Autonomy, of patient
  - brain death and, 1097
  - cardiac arrest and, 154–155
  - persistent vegetative and minimally conscious states, 1118
- Ethionamide, 617*t*, 618, 1034
- Ethosuximide, 320–321, 578, 580, 611, 1009*t*
- Ethylmalonic encephalopathy, 357*t*
- Eustachian valve, 73
- Euthanasia, 1112, 1119
- Evaporative cooling, 668–669
- Evaporative heat loss, 661
- Everolimus, 797
- Ewing battery, 311
- Excessive daytime sleepiness
  - differential diagnosis of, 921, 922*t*
  - in idiopathic hypersomnias, 923
  - in narcolepsy, 920
  - in obstructive sleep apnea, 924
  - Parkinson disease and, 1109
  - in shift work disorder, 929
  - treatment of, 922
- Exertional heat stroke, 665, 668
- Exertional syncope, 81, 133
- *Exophiala dermatitidis*, 803, 811
- Experimental allergic encephalomyelitis, 761–762
- Exploding head syndrome, 935
- *Exserohilum rostratum*, 803
- Extracorporeal circulation, 43, 47*f*
  - neurologic sequelae of, 46–49
- Extracorporeal membrane oxygenation (ECMO), 46–47, 60, 1013–1014
  - neurologic complications of, 48–49
- Extradural myeloma, 449
- Extramedullary myeloblastoma, 448
- Extraocular muscles
  - lateral, 426*t*
  - limitation of movement, 426*t*
  - medial, 426*t*
  - thyroid eye disease, 426*t*, 430
  - weakness of, 430
- Extreme delta brush, 1015
- Extrinsic nervous system, 217–219, 219*f*
- Extrinsic neurologic disease and gut dysmotility, 231–232
- Eye disorders
  - abducens nerve palsy, 429
  - abnormal movements, 431–433
  - afferent, 415–424
    - idiopathic intracranial hypertension, 422–423, 423*f*
    - optic neuropathy. *See* Optic neuropathy
    - papilledema, 422, 422*f*, 422*t*
    - retrochiasmal vision loss, 423–424
  - efferent
    - alternate cover test for, 424
    - clinical assessment of, 424–426
    - diplopia, 424, 430–431
    - internuclear ophthalmoplegia, 429
    - Maddox rod, 424
    - Miller Fisher syndrome, 429
    - motility examination, 425
    - neuromuscular junction dysfunction, 429–430
    - nystagmus, 431–433
    - ocular dysmotility, 427
    - ocular misalignment, 424
    - saccadic intrusions, 433
  - ischemic disorders that cause, 420*t*
  - manifestations of, 416*t*
  - oculomotor nerve palsy, 427–428
  - pupil
    - afferent defect of, 434
    - anatomy of, 433–434
    - anisocoria, 132, 428, 434–436
    - Argyll Robertson, 434, 706–707
    - examination of, 433
    - light response, 434
    - near response, 434
    - swinging flashlight test of, 434
    - tonic, 434, 436
  - syphilis involvement, 355
  - thyroid-associated ophthalmopathy, 296–298, 297*f*
  - trochlear nerve palsy, 428–429
- "Eye-of-the-tiger" sign, 446
- Ezetimibe, 172, 620, 621*t*

F

- Fabry disease
  - cutaneous manifestations of, 366*t*
  - description of, 127, 267, 347–349
  - polyneuropathy in, 1063*t*, 1073
  - stroke in, 348*t*, 349
- Facial nerve. *See also* Bell palsy
  - dysfunction of, 401
  - palsy of, 310–311, 327, 406–407, 406*f*, 596, 871, 880
- Faciobrachial dystonic seizures (FBDS), 507
- Factor deficiencies and stroke, 176–177
- Factor III subunit A deficiency, 348*t*
- Factor V Leiden, 177, 472
- Factor V Leiden homozygote mutation, 471
- Factor VIII, 460, 473
- Factor IX deficiency, 461
- Failure to wean from mechanical ventilation, 998
- Falls. *See also* Ataxia
  - dementia and, 1108

  - prevention of, 1108
  - progressive supranuclear palsy and, 1102, 1108
  - risk factors for, 1108
- Familial amyloid polyneuropathy of Portuguese type, 127
- Familial hypercholesterolemia, 348*t*
- Familial hypocholesterolemia, 208–209
- Fatty acid oxidation disorders, 1084
- Fecal incontinence, 224–225, 228
- Felbamate, 255, 321, 581, 1009*t*, 1010*t*, 1011, 1017, 1027*t*, 1039*t*
- Female orgasm, 561, 561*f*
- Female sexual arousal disorder, 563
- Female sexual function, 34–35, 557–563
- Femoral nerve
  - anatomy of, 31–32
  - neuropathy of, 31–32, 49, 264
  - perioperative compression of, 984*f*
- Fetal malformations and maternal epilepsy, 579
- Fetus
  - cytomegalovirus infection of, 590
  - malformations of, 579–580
  - maternal epilepsy effects on, 579
- Fiberoptic endoscopic evaluation of swallowing, 219–221
- Fibrous dysplasia, 409, 410*f*
- Fibular neuropathy, 983–984
- FilmArray Meningitis/Encephalitis panel, 685
- Fingolimod, 324, 614, 800
  - during pregnancy, 593
- Fite-Faraco staining, 730
- Flakka, 640
- Flapping tremor, 191, 253, 611, 1040
- “Flashbacks”, 643
- Flavivirus, 687, 744*t*, 745*t*, 753, 755, 1040
- Flocculus, 427, 431–432
- Fluconazole, 617–618
  - for CNS candidal infection, 844
  - for coccidioidal meningitis, 818
  - for cryptococcal meningitis, 779, 813, 815–816, 842
  - for granulomatous amebic encephalitis, 831
- Fluconazole prophylaxis, 792
- Flucytosine, 410, 779, 792, 815–818, 831, 842, 844
- Fludarabine, 121, 506*t*, 522*t*, 523, 523*t*, 606, 1070
- Fludrocortisone, 132, 141*t*, 142–143, 311
- Fluid-attenuated inversion recovery (FLAIR), 245*f*, 259–260, 686
- Flumazenil, 605*t*, 641, 980, 1089, 1094
- Fluoroquinolones, 410, 617*t*, 619–620, 724, 780, 968*t*, 1014*t*, 1021
- Flynn–Aird disease, 362*t*, 366*t*
- Focal dystonia, 1025
- Focal ischemic neuropathy, 1063–1065
- Focal neurologic injury, cardiac manifestations of, 163–164
  - cardiac rhythm, disturbances of, 164–165
    - arrhythmias, 164–165
    - heart rate variability and baroreceptor reflex sensitivity, 165
  - electrocardiographic (ECG) abnormalities, 163–164
    - Q waves and U waves, 164
    - QT prolongation, 163–164, 164*f*
    - repolarization abnormalities, 164
- Focal paranasal sinus infections and headache, 1050
- Folate deficiency, 238–240
  - antituberculous therapy and, 239, 239*t*
  - clinical manifestations of, 239, 444
  - diagnosis of, 236*t*, 239
  - etiology of, 238–239
  - risk factors for, 239, 239*t*
  - treatment of, 236*t*, 240
- Folate supplementation during pregnancy, 579–580
- Folic acid, 240
- Folinic acid, 827
- Fontan procedure, 53–54
- Food-borne botulism, 1074–1075
- Foramen ovale, patent, 68–69, 73, 80–81, 91, 474
- Forced expiratory volume in 1 second (FEV1), 7
- Forced vital capacity (FVC), 7, 971–972
- Foscarnet, 335*t*, 605*t*, 743*t*, 751*t*, 757, 759, 780–781, 1059
- Fosphenytoin, 971, 1012
- Fowler syndrome, 547–548
- Fractures
  - osteoporotic, 377–378
  - spine, 390
  - vertebral, 378
- Frenzel lenses, 431
- Friedreich ataxia, 74, 208, 242
- Frisen Scale, 422*t*
- Frontotemporal dementia, 387–389, 1101–1102, 1102*f*, 1105*t*
- Frovatriptan, 1052
- Fucosidosis, 366*t*
- Functional dizziness, 943–944
- Functional dystonia, 942–943, 942*t*
- Functional excess movements, 942
- Functional magnetic resonance imaging (fMRI), 159, 162, 558, 561, 945–946, 956
- Functional movement disorders, 944
  - phenotype-specific diagnostic criteria, 944
  - voxel-based morphometry and, 944
- Functional neurologic disorders (FNDs), 939
  - axial disorders, 943
  - clinical features of, 941–944
  - diagnostic criteria, 944
  - dystonia, functional, 942–943, 942*t*
  - etiology, 944
  - functional dizziness, 943–944
  - gait, functional, 942*t*, 943
  - motor disorders, 942–943
  - neurologic examination in, 945
    - positive signs on, 942*t*
  - nonepileptic seizures (NESs), 943
  - parkinsonism, functional, 942*t*, 943
  - pathophysiology, 944–945
  - psychologic factors, 944
  - sensory symptoms, 942*t*, 943
  - sensory symptoms, functional, 942*t*, 943
  - speech and voice disorders, 942*t*, 943
  - treatment, 945–946
    - comorbid depression/anxiety, 946
    - delivery of the diagnosis, 945
    - motor rehabilitation, 946
    - multidisciplinary approach, 946
    - psychologic treatment, 945–946
  - tremor, functional, 942–946, 942*t*
  - visual loss, 943–944
  - weakness, 942, 942*t*
- Functional neurosurgery, 987
- Fungal infections
  - *Aspergillus* spp., 804–805, 804*t*, 810, 814
  - *Blastomyces dermatitidis*, 804*t*, 808–809
  - *Candida* meningitis, 817–818
  - *Candida* spp., 804*t*, 809–810, 814
  - in central nervous system, 803–819
  - of cerebrospinal fluid shunts, 804*t*, 805, 818
  - coccidioidal meningitis, 818
  - *Coccidioides immitis*, 804*t*, 807–808
  - *Coccidioides posadasii*, 807–808

Fungal infections (*Continued*)
  complications, 816–817
  cryptococcal meningitis, 776*t*, 779, 804–807, 812, 814–817
  Cryptococcus gatti, 806–807
  Cryptococcus neoformans, 804*t*, 806–807
  diagnosis of, 812–814, 812*t*, 813*t*
  features of, 804*t*
  Histoplasma capsulatum, 804*t*, 808
  host factors, 804–806
  hyalohyphomycosis, 811
  imaging of, 814
  immune reconstitution inflammatory syndrome (IRIS) and, 806
  meningitis, 722*t*, 747, 799, 803, 806, 812, 813*t*, 814, 841*t*, 959
  movement disorders and, 1030
  mucormycosis, 810–811, 818
  Paracoccidioides brasiliensis, 804*t*, 809
  pathogens, 803–804
  Penicillium marneffei, 809
  phaeohyphomycosis, 811
  in post-transplantation period, 789–790
  risk factors for, 804–805
  Scedosporium species, 804*t*, 811
  serologic tests for, 813
  Sporothrix schenckii, 804*t*, 809, 814
  surgical treatment of, 818–819
  transplantation-related, 805
  treatment of, 814–819
Fungal meningitis, 722*t*, 747, 799, 803, 806, 812, 813*t*, 814, 841*t*, 959
Fusional maldevelopment nystagmus, 433
F-wave chronodispersion, 738

G

GABA$_A$ receptor, 502, 508, 751, 761, 1014*t*, 1020–1021
Gabapentin, 579, 606, 1010–1011, 1018, 1051, 1053*t*
  dose adjustments for, 1010*t*
  neuropathic pain treated with, 315
  pharmacokinetics of, 1009*t*
  for restless legs syndrome, 932*t*
Gabapentin enacarbil, for restless legs syndrome, 932*t*
GAD65 antibodies, 1016
Gadolinium contrast, 577–578, 952
Gait, functional, 942*t*, 943
Gait ataxia. *See* Ataxia
Galactomannan, 814
Galvanic skin response, 139–140
Gambian trypanosomiasis, 829
Gamma hydroxybutyrate, 640–641
Ganciclovir, 605*t*, 743*t*, 751*t*, 759, 780–782, 788, 792, 1059
Ganglionic acetylcholine receptors, antibodies to, 230
Ganglionic receptor-binding antibodies, 229
Gangliosides, 452, 619, 1069
Garin–Bujadoux–Bannwarth syndrome, 707–708, 712
Gasserian ganglion syndrome, 483*t*
Gastric emptying, delayed
  in diabetes mellitus, 221
  in Parkinson disease, 226
Gastrointestinal disorders, 201–202
  bariatric surgery, 201–202
  celiac disease (CD). *See also* Celiac disease (CD)
    ataxia, 203–204
    characteristics of, 203
    epilepsy and, 204
    movement disorders and, 1031
    myopathy and, 204
    neurologic dysfunction associated with, 203
    peripheral neuropathy, 204
    prevalence of, 203
  hepatic disorders. *See* Hepatic disorders
  inflammatory bowel disease, 204–205, 205*t*
    cerebrovascular disease, 206
    demyelinating disease, 206
    myelopathy, 206
    myopathy, 206
    peripheral neuropathy, 205–206
  malabsorption syndromes, 208–210
    copper deficiency, 202, 210, 240–241, 1064*t*, 1072
    familial hypocholesterolemia, 208–209
    pellagra, 209–210
    tropical sprue, 209
    vitamin E deficiency, 208
    Wernicke encephalopathy (WE), 209
  Whipple disease, 207–208, 207*t*
Gastrointestinal motility disorders. *See also* Gut dysmotility
  algorithm for, 232*f*
  management of, 233
  surgery for, 233
Gastrointestinal neuropathy, 311
Gastrointestinal symptoms
  chronic intestinal pseudo-obstruction, 221–222, 223*t*
  constipation, 222–223
  diarrhea, 223–224
  dysphagia, 219–221
  fecal incontinence, 224–225
  gastroparesis, 221, 222*f*
Gastroparesis, 221, 222*f*, 229
  symptoms of, 221
Gaucher disease, 378*t*, 467–468, 868
Gaze deviation, 44–45, 67, 427
Gaze paralysis, 44–45
Gaze-evoked nystagmus, 429, 431–432
GBA1 mutation carriers with Parkinson disease, 467
Gefitinib, 481, 492, 522*t*, 523*t*
Gemcitabine, 522*t*, 523*t*, 525
General anesthesia
  coma after, 979–981
  delayed awakening after, 979–981
  delirium after, 981
  eustachian tube obstruction after, 984
  hypothermia and, 667*t*
  multiple sclerosis and, 967
  in neurocritical care unit, 988–989
  in patients with neurologic disease, 986–988
  perioperative headache and, 986
  perioperative rigidity and, 985
  perioperative seizures and, 985–986, 986*t*
  postoperative neurologic deficits, 980*t*, 981–982
General paresis of insane (GPI), 354, 707, 1103
Genetics of stroke, 185–186
Gerstmann–Straussler–Schenker disease, 759
Gestational epilepsy, 321
Giant cell arteritis (GCA), 36–37, 291, 368–369, 415, 420–421, 428, 900, 902–904
  hypothyroidism and, 291
Gigantism, 331
Glanzmann thrombasthenia, 348*t*, 463
Glatiramer acetate
  during pregnancy, 593
Glial fibrillary acidic protein (GFAP), 49, 674–675
Gliomas, 16, 276, 306*t*, 323, 330*t*, 339*t*, 344–345, 347, 356, 408, 433, 453, 478, 526, 535, 535*t*, 567, 582

Global hypoxia-ischemia, 49, 1024–1025, 1033–1034
Global neurologic injury, cardiac manifestations of, 162–163
  cardiac biomarkers of neurologic injury, 162
    B-type natriuretic peptide (BNP), 163
    creatine kinase (CK)-MB, 162
    troponin, 162–163
  reduced left ventricular function, 162
  regional wall motion abnormalities, 162
Glossopharyngeal nerve, 126, 220*t*, 226, 872
Glucocorticoids, 1022. *See also* Corticosteroids
Glucose metabolism disorders, 1019
Glutamic acid decarboxylase 65-kilodalton isoform (GAD65), 1016
Gluten ataxia, 203–204
Gluten neuropathy, 204
Gluten sensitivity, 203
Gluten-sensitive enteropathy, 229
Glycogen storage disease, 378, 1084
Glycogen synthase kinase 3 (GSK-3), 314
Glycopyrrolate, 227–228, 1116
Gnathostoma spinigerum, 822*t*
Gnathostoma spp., 835
Gnathostomiasis, 835
Gonadotropin-releasing hormone agonists, 325–326
Gottron rash/sign, 1079
Gowers sign, 380
G-protein coupling process, 158
Gradenigo syndrome, 399
Graft-versus-host disease (GVHD), 791–793
Granulocytic sarcoma, 448
Granulomatosis with polyangiitis (GPA), 900–901. *See also* Wegener granulomatosis
Granulomatous amebic encephalitis (GAE), 830
Granulomatous amebic meningoencephalitis, 829
Graves disease, neurologic complications of, 291–299, 1051
Graves ophthalmopathy. *See* Thyroid-associated ophthalmopathy
Gray platelet syndrome, 463
Greater vestibular glands, 34–35
Growth hormone, 252, 328, 328*t*, 331–332, 334*t*, 535*t*, 604, 623, 759, 1077
Guanidinosuccinic acid, 252
Guillain–Barré syndrome, 13, 228, 260, 460, 755, 760–761, 797, 902, 997, 999, 1058*t*, 1063*t*, 1064*t*, 1069–1070
  anemia and, 442
  approach to, 763
  arsenic neuropathy versus, 654–655
  assessment of, 1069
  autonomic involvement in, 128
  bladder dysfunction in, 547
  disability and, 1069
  drugs associated with, 618–619, 623–624
  infections and, 1069–1070
  influenza vaccine and, 862
  laboratory tests, 763
  Miller Fisher syndrome and, 429
  neuroborreliosis and, 712
  in pregnancy, 596
  preoperative considerations, 972
  respiratory dysfunction caused by, 8, 13
  surgery as trigger for, 972
  symptoms of, 1069
  treatment of, 128, 506*t*, 1069–1070
  viruses associated with, 763*t*
  visceral involvement in, 228
Gupta-Lang criteria, 944
Gut, layers of, 219
Gut dysmotility. *See also* Gastrointestinal motility disorders
  Alzheimer disease and, 225
  amyloid neuropathy and, 230
  amyotrophic lateral sclerosis and, 226
  autoimmune neuropathies and, 230–231
  autonomic epilepsy and, 226
  autonomic system degenerations that cause, 227
  brain diseases that cause, 225–227
  brainstem lesions and, 227
  chronic sensory and autonomic neuropathy, 230
  diabetes mellitus and, 229
  extrinsic neurologic disease and, 231–232
  head injury and, 226
  human immunodeficiency virus (HIV) infection, 230–231
  idiopathic orthostatic hypotension and, 227
  migraine and, 226
  multiple sclerosis, 228
  multiple system atrophy and, 227–228
  muscle diseases that cause, 231–232
  neurofibromatosis and, 230
  neuromyelitis optica, 228–231
  pandysautonomias and, 227
  paraneoplastic neuropathy, 229
  parkinsonism and, 225–226
  peripheral neuropathy and, 228–231
  porphyria and, 230
  postpolio dysphagia and, 226
  postural orthostatic tachycardia syndrome and, 227
  spinal cord injury and, 227–228
  stroke and, 225

H

H1N1 influenza, 458
H1N5 influenza, 458
H5N1 virus, 862
Haemophilus influenzae type b
  bacterial meningitis caused by, 683–684, 691
  neurocutaneous manifestations of, 352*t*
  otitis media complications caused by, 399–400
Hallucinogens, 608, 643
Halothane, 966, 972–973
HAND. *See* HIV-associated neurocognitive disorder
Hartnup disorder/syndrome, 246, 270, 362*t*, 364
Hashimoto encephalopathy, 299–301, 1016, 1031, 1035–1037, 1041
Hashimoto thyroiditis, 291, 299–300, 1016, 1031
Head
  injuries to. *See also* Postconcussion syndrome; Traumatic brain injury (TBI)
    gut dysmotility and, 226
    sexual dysfunction and, 565
  trauma of. *See also* Trauma; Traumatic brain injury (TBI)
    brain abscess caused by, 692–693, 695*t*
    parkinsonism caused by, 1045
Headache, 1047. *See also* Migraine
  anesthesia and, 986
  aseptic meningitis, 604
  asthma and, 1051
  autoimmune disorders and, 1052
  Behçet disease and, 906
  brain abscess and, 693
  caffeine withdrawal and, 970, 1051
  cardiovascular disease and, 1049
  cerebrovascular disease and, 1050

Headache (*Continued*)
  chemotherapeutic agents and, 523*t*
  chronic kidney disease and, 1051
  coarctation of the aorta and, 38
  comorbidity with general medical illness, 1047–1049, 1048*t*
  in dialysis disequilibrium syndrome, 1051
  dialysis dysequilibrium syndrome and, 262
  dialysis headache, 1051
  drug-induced, 604
  in elderly, 1054
  in end-stage renal disease (ESRD), 1051–1052
  focal paranasal sinus infections and, 1050
  giant-cell arteritis (GCA) and, 903
  in hemodialysis patients, 1051
  hepatic disease and, 1052
  HIV and, 1050
  hypertension and, 1049–1050
  hypnic, 1054
  infectious disease and, 1050
  insomnia and, 937
  intracranial hypotension and, 970
  liver disease and, 1052
  lumbar puncture and, 956, 970, 986*t*, 1050
  medication-overuse, 604, 970
  medications used in management of, 1049
  myelography and, 956
  neoplastic disease and, 1052
  obesity and, 1047, 1051
  obstructive sleep apnea and, 19, 937
  Paget disease of bone and, 384
  perioperative, 986, 986*t*
  postoperative, 969, 970*t*, 986
  psychiatric disorders and, 1053–1054
  pulmonary disease and, 1051
  renal disease and, 1051–1052
  rheumatoid arthritis and, 1052
  secondary, 969, 970*t*
  sleep disorders and, 937, 1047–1048
  substance abuse and, 1054
  systemic lupus erythematosus and, 888
  temporal arteritis and, 902–903
  thyroid disorders and, 1051
  transplantation and, 1052–1053
  and unruptured cerebral aneurysms, 106
  vascular, 604
  viral meningitis and, 742
Hearing loss
  autoimmune, 408
  cisplatin and, 527
  conductive, 392–393
  in diabetes mellitus, 408
  endocrine disorders and, 408
  environmental causes of, 411
  hyperlipidemia and, 408
  lumbar puncture and, 956
  metabolic disorders and, 408
  in mucopolysaccharidoses, 408
  myelography and, 956
  noise-induced, 411
  postoperative, 984–985
  renal failure and, 408
  salicylates and, 411
  sensorineural
    aging and, 412–413
    description of, 392–393
    Lyme disease and, 406–407
    noise exposure and, 411
    systemic lupus erythematosus and, 408
Heart. *See cardiac and specific disorders*
Heart disease, structural and syncope, 81–83
Heart failure with reduced ejection fraction, 75
Heart rate
  postural change in, 134–135
  Valsalva maneuver and, 135–137, 136*f*
  variation in, during deep breathing, 137, 137*f*
Heart rate variability, 165
Heat exhaustion, 665
Heat stress disorders, 665
Heat stroke, 667–668
Heavy chain deposition disease, 451–452
Heavy metals
  arsenic, 129, 366*t*, 614, 648, 654–655, 654*f*, 1036*t*, 1039*t*, 1064*t*, 1065*t*, 1073, 1083
  intoxication with, 1039–1040
  lead, 652–654, 1036*t*, 1039*t*, 1064*t*, 1073
  manganese, 655–656, 656*f*, 1036*t*
  mercury, 103, 129, 655, 1027*t*, 1036*t*, 1039*t*, 1042, 1063*t*, 1064*t*
  neuropathies associated with, 14, 1073
  occupational neurotoxin disorders caused by, 652–656
Heerfordt disease, 407
HELLP syndrome, 465, 584, 599
Helminthic infections
  cestodes
    cysticercosis, 831–833
    echinococcosis, 833–834, 833*f*
    sparganosis, 833–834
  characteristics of, 822*t*
  description of, 821
  life cycles, 821
  nematodes
    gnathostomiasis, 835
    loiasis, 836
    onchocerciasis, 836
    strongyloidiasis, 834, 834*f*
    trichinosis, 834
    visceral larval migrans, 835–836
  trematodes
    paragonimiasis, 837
    schistosomiasis, 836–837
Hematologic disorders
  anemia. *See* Anemia
  cerebellar hemangioblastoma, 456
  cold agglutinin disease, 445–446
  cryoglobulinemia, 446
  eosinophilic syndromes, 457–458, 458*t*
  essential thrombocythemia, 457
  heavy chain deposition disease, 451–452
  hemophagocytic lymphohistiocytosis, 458–459
  intracranial hemorrhage and, 448–449
  kernicterus, 446
  leukemia. *See* Leukemia
  light chain deposition disease, 451–452
  lymphoma. *See* Lymphoma
  macroglobulinemia, 446, 449, 451–453, 506, 517, 1071
  macrophage activation syndrome, 459
  myelofibrosis, 457
  myelomatosis, 449–451
  paraproteinemias, 452–453
  paroxysmal nocturnal hemoglobinuria, 445
  polycythemia, 455–456
  pseudopolycythemia, 456–457
  red cell abnormalities, 446–447

  sickle cell disease, 444–445
  thalassemia, 445
Hematologic disorders and stroke, 175–176
  antiphospholipid antibody syndrome, 175–176
  cryoglobulinemia, 178
  factor deficiencies, 176–177
  inherited thrombophilias, 177–178
  sickle cell anemia, 178
  Sneddon syndrome, 176
Hematologic malignancies
  neurologic complications of therapies for, 459–460
    checkpoint inhibitors, 459–460
    chimeric antigen receptor (CAR) T-cell therapies, 459
Hematopoietic cell transplantation (HCT), 791–792
  early complications, 791–792
  intermediate complications, 792
  late complications, 793
Hemiballism, 113, 323, 1024, 1030, 1032
Hemichorea, 296, 304, 1024, 1030–1031
Hemidystonia, 1024, 1032
Hemifacial spasm, 385–386
Hemochromatosis, 337*t*, 366*t*, 1040, 1043
Hemodialysis, 128, 253–267, 280, 571, 606, 669, 1008, 1009*t*, 1010*t*, 1021, 1026, 1043, 1051, 1063, 1071, 1073
Hemodialysis, headache and, 1051
Hemodilution, extracorporeal circulation and, 47–48
Hemoglobin SC, 444–445
Hemoglobin SS, 444
Hemolytic-uremic syndrome
  characteristics of, 466
  in children, 466
  familial, 466
  neurocutaneous manifestations of, 348*t*, 357*t*
  postpartum, 599
Hemophagocytic lymphohistiocytosis (HLH), 362*t*, 458–459, 1091
Hemophilia A, 460–461
Hemophilia B, 461
Hemophilic arthropathy, 460–461
Hemorrhage
  and ECMO, 48–49
  intracerebral. *See* Intracerebral hemorrhage (ICH)
  intracranial. *See* Intracranial hemorrhage
  intratumoral, 478*f*
  subarachnoid. *See* Subarachnoid hemorrhage
Hemorrhagic disorders
  acquired hemophilia A, 462
  clotting factor deficiencies, 461
  disseminated intravascular coagulation, 448–449, 463–465, 464*t*
  Gaucher disease, 467–468
  hemolytic-uremic syndrome, 348*t*, 357*t*, 466–467, 599
  hemophilia A, 460–461
  hemophilia B, 461
  of the newborn, 462
  platelet function disorders, 463
  thrombocytopenia, 462–463
  thrombotic thrombocytopenic purpura, 465–466
  von Willebrand disease, 461
Hemorrhagic leukoencephalitis, acute, 762
Hemorrhagic stroke, 10, 875, 1024. *See also* Intracerebral hemorrhage (ICH); Intracranial hemorrhage; Stroke
  cardiac arrhythmias after, 167
  in children with congenital heart disease, 59
  detrusor underactivity and, 544
  QT prolongation after, 163–164
  renal disease and, 258
  in systemic lupus erythematosus, 888
  ventricular arrhythmias after, 165
Hemorrhagic stroke in infective endocarditis, 92–95
  clinical presentation, 93–94
  patients, evaluation of, 94–95
    brain imaging, 94–95
    cerebrospinal fluid (CSF) examination, 95
    echocardiography, 95
    vascular imaging, 94–95
  seizures, 94–95
  treatment of, 97
  intraparenchymal hemorrhage, 97
  mycotic aneurysms, 97
Heparin-induced thrombocytopenia, 462
Hepatic cirrhosis, 1010
Hepatic disorders, 210–214. *See also* Hepatic encephalopathy
  antiseizure medications and, 1010–1011
  and headache, 1052
  seizures in, 1010–1011
  Wilson disease, 211–214. *See also* Wilson disease
Hepatic encephalopathy
  in acute liver failure, 193, 196, 199
  astrocyte swelling in, 196–197
  chronic progressive, 192–193
  in cirrhosis, 194, 197–199
  clinical features of, 191–192
  Continuous Reaction Time Test (CRT) and, 195
  critical flicker frequency and, 194–195
  definition of, 191
  diagnosis of, 193–194
  electroencephalography for, 195–196, 195*f*
  hepatic myelopathy, 194–196
  Inhibitory Control Test (ICT) for, 195
  laboratory studies, 196
  minimal, 193–196, 198
  neuroimaging for, 196
  pathophysiology of, 196–197
  seizures in, 1009–1010
  transjugular intrahepatic portosystemic shunting for, 192
  treatment of, 197–198
  West Haven criteria for, 192*t*
Hepatic failure. *See* Liver failure
Hepatic myelopathy, 194–196, 199
Hepatic transplantation, 793–795
Hepatitis B
  definition of, 863
  polyarteritis nodosa and, 901, 1066
  vaccine for, 863
  vasculitic neuropathy, 1066
Hepatitis C
  description of, 211
  essential mixed cryoglobulinemia and, 1067
  HIV and, 772
  peripheral neuropathy in, 1067
Hepatocerebral disorders, 632
Herbicides and parkinsonism, 659
Hereditary hemorrhagic telangiectasia, 348*t*, 349–350
Hereditary neuralgic amyotrophy, 595
Hereditary sensory neuronopathy, 1061
Hereditary spherocytosis, 445
Hereditary thrombophilia
  antithrombin III deficiency, 471
  arterial thrombosis and, 473–474
  description of, 471
  factor V Leiden, 472
  protein C deficiency. *See* Protein C, deficiency of

Hereditary thrombophilia (*Continued*)
  protein S deficiency. *See* Protein S, deficiency of
  prothrombin G:A 20210 mutation, 472
  stroke and, 473
Hering–Breuer reflex, 4–5
HERMES collaboration, 78
Heroin, 642, 1020
Herpes simplex encephalitis
  autoimmune encephalitis following, 761
Herpes simplex virus, 1059
  Bell palsy and, 405–406, 406*f*
  encephalitis caused by, 686–687, 746, 749–751, 758–759, 1037
  hematogenous spread of, 741
  in immunocompromised patients, 757
  meningitis caused by, 686
  neonatal infection with, 590
  type 1, 743*t*, 749
  type 2
    characteristics of, 743*t*, 746, 749
    meningitis caused by, 746, 748
    treatment of, 748
Herpes zoster oticus, 406
Herpes zoster-related vasculitis, 1040
2,5-Hexanedione, 652
Hiccup, 10
High–high low–low rule and skew deviation, 427
Highly active antiretroviral (HAART) therapy, 623
High-pressure neurologic syndrome, 1041
Hirschberg method, 424
Histiocytic reticulosis, 352*t*, 366*t*
Histoplasma capsulatum, 790, 804*t*, 808, 813
HIV-associated dementia, 768, 768*t*, 769*f*, 775, 1103
HIV-associated neurocognitive disorder
  adjunctive therapies for, 769–770
  asymptomatic neurocognitive impairment, 767–768, 768*t*
  classification of, 768*t*
  cutaneous manifestations of, 359
  definition of, 767–770
  dementia, 359, 768, 768*t*, 769*f*, 775
  diagnosis of, 769, 770*f*
  management of, 769, 770*f*
  mild neurocognitive disorder, 768, 768*t*
  neuropsychologic tests, 767
  treatment of, 769–770
HLA genes, 729
HLA-B27, 389–390
HMG-CoA reductase inhibitors (statins), 172
Hodgkin disease, 128, 453, 508–511
Hoffmann syndrome, 289
Holmes tremor, 1040–1041
Holmes–Adie syndrome, 130, 140, 436
Holocarboxylase synthetase deficiency, 357*t*
Holotranscobalamin, 442
Homeostatic process, circadian rhythm and, 914
Homocysteine
  folate deficiency and, 239
  and stroke, 172–173
  vitamin B$_{12}$ deficiency and, 442–444
Homocystinuria, 173, 348*t*, 350, 357*t*
Hoover sign, 942, 945
Hormone replacement therapy
  dementia and, 325
  neoplasms and, 323–324
  postmenopausal, 183
  stroke and, 320
  subarachnoid hemorrhage and, 320
Horner syndrome, 45
  ara-C and, 524–525
  brachial plexus lesions and, 494, 1061
  description of, 435
  dysautonomia and, 132
  after epidural anesthesia, 985
  radiation and, 494–495, 534
  skull base syndromes and, 483*t*
HTLV-1. *See* Human T-lymphocytic virus type I
HTLV-associated myelopathy/tropical spastic paraparesis, 782
Hu antibodies, 505, 508–510
Huffing and puffing sign, 943
Human herpesvirus, 6, 743*t*, 756
Human immunodeficiency virus, 74–75. *See also specific HIV entries*
  aging with, 773
  antiretroviral therapy for
    central neurotoxicity of, 774
    CNS-penetration effectiveness of, 771*t*
    life expectancy affected by, 773
    mechanism of action, 767–774
    progressive neurologic disease from, 771–772
  aseptic meningitis and, 775
  CD4$^+$ T cells, 766
  in central nervous system
    blood–brain barrier effects on, 770–771
    description of, 766–767
    effects of, 774–775
    targeted treatment of, 770–771
  cerebrospinal fluid findings in, 771–772, 775
  cognitive impairment caused by, 772, 1103
  course of, 766*f*
  CSF HIV RNA, 771
  dementia associated with, 768, 768*t*, 769*f*, 775
  distal sensory polyneuropathy and, 781
  encephalitis, 1018
  end-organ effects of, 767
  endothelial activation caused by, 773
  essential mixed cryoglobulinemia and, 1067
  global prevalence of, 765–766
  gut dysmotility and, 230–231
  and headache, 1050
  hepatitis C and, 772
  inflammatory polyneuropathies and, 781–782
  ischemic stroke in, 773
  leprosy and, 738–739
  meningitis caused by, 746
  muscle disorders and, 782
  myoclonus and, 1037
  myopathy and, 1078
  nervous system and, 766–767
  neurocognitive disorder. *See* HIV-associated neurocognitive disorder
  neurocutaneous manifestations of, 359
  neurosyphilis and, 707
  opportunistic infections
    cryptococcal meningitis, 776*t*, 779
    cytomegalovirus encephalitis, 776*t*, 780
    diagnosis of, 776*t*, 777*f*
    overview of, 775–781
    primary CNS lymphoma, 776*t*, 778–779
    progressive multifocal leukoencephalopathy, 757–758, 775–777, 776*t*, 780
    toxoplasmosis, 776*t*, 777–778, 778*f*
    tuberculous meningitis, 776*t*, 780–781
  otoneurologic manifestations of, 407

  - parkinsonism and, 1043–1044
  - peripheral neuropathies associated with, 781–782
  - polymyositis and, 782, 1078
  - prevalence of, 765–766
  - pyomyositis and, 782
  - seizures and, 1018
  - sensory neuronopathy and, 1060
  - spinal cord disease associated with, 781
  - stages of, 766
  - stroke and, 773–774
  - treatment of, 746, 1018
  - tremor and, 1040
  - tuberculous meningitis and, 720
  - vacuolar myelopathy in, 781
- Human T-lymphocytic virus type I (HTLV), 782–783, 847
- Humanized anti-interleukin-5 antibodies, 458
- Hunt Hess score, 162–163
- Hunter syndrome, 408
- Huntington disease
  - anesthesia in, 988
  - dysautonomic symptoms in, 127
  - during pregnancy, 591
  - respiratory function in, 2
  - sexual dysfunction in, 567
- Huntington disease-like syndrome, 447
- Hurler syndrome, 408
- Hyalohyphomycosis, 811
- Hydrocephalus
  - acute decompensating, 873
  - aqueductal stenosis with, 748
  - brain metastases and, 477–478
  - coma and, 1088*t*
  - communicating
    - in bacterial infections, 351, 690, 691*f*
    - in cryptococcal meningitis, 779
    - dementia and, 1100, 1104, 1104*f*
    - in neoplastic meningeal involvement, 266, 447, 490–492, 509, 850
    - in sarcoidosis, 870–871, 873, 875, 881, 883
    - simulating parkinsonism, 1045
    - in tuberculous meningitis, 179–180, 718–725, 844
  - fungal meningitis and, 789, 805, 808, 814, 818–819, 842
  - hyperthermia and, 662*t*, 663
  - intracranial hemorrhage and, 107, 109
  - normal-pressure, 263, 359, 531*t*, 533, 544–545
  - obstructive, 107, 109, 329, 384, 386, 590, 722, 808
  - osteopetrosis and, 382
  - otitic, 399–400
  - Paget disease and, 384, 386
  - parasitic CNS infection and, 822*t*, 826, 832, 837, 846, 1044
  - pituitary disease and, 448
  - in sarcoidosis, 873, 881
  - syndrome of inappropriate ADH secretion, 335–336, 336*t*
  - treatment of, 724, 881
- Hydrocodone, 1036*t*, 1052
- Hydroxychloroquine, 208, 614, 617, 621*t*, 624, 889, 892, 897, 1083
- Hydroxykynreniuria, 362*t*
- Hydroxykynureninuria, 364
- 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), 1083
- 5-Hydroxytryptophan, 1033–1034
- Hydroxyurea, 444–445, 458
- Hyperactive delirium, 967–968
- Hyperacusis, 954
- Hyperammonemia, 196, 199, 793, 980, 1011
- Hypercalcemia, 258, 279, 335, 335*t*, 381, 450–451, 500*t*, 868*t*, 877, 883, 968*t*, 1019, 1040, 1089*t*, 1090
- Hypercapnia, 18
  - respiratory failure, severe hypercapnia due to, 48
- Hypercholesterolemia, 116–118, 348*t*, 1100
- Hypercoagulability, 181, 183, 319–320, 350, 445, 469, 500*t*, 638, 670, 760, 773, 1092
  - in pregnancy, 583–584
  - sex hormone–induced, 319–320
- Hypercortisolism, 332, 338–339, 339*t*
- Hypereosinophilic syndrome, 457
- Hyperestrogenemia, 327
- Hyperexcitability, peripheral nerve, 519
- Hyperglycemia. *See also* Diabetes mellitus
  - in children with type 1 diabetes, 312
  - following stroke, 172
  - intraoperative, 974
  - myoclonus and, 1034
  - nonketotic hyperosmolar, 1034
  - phenytoin and, 1019
- Hyperhomocysteinemia, 172–173, 239, 258, 420, 442, 471, 473
- Hyper-IgE syndrome, 348*t*
- Hyperinsulinemia, 314
- Hyperkalemia, 167, 278, 1051, 1082
- Hyperkalemic periodic paralysis, 278, 339, 1058*t*
- Hyperkinetic disorders, 12
- Hyperkinetic movements, 60
- Hypermagnesemia, 280
- Hypermetropia, 614
- Hypernatremia, 276–277
  - body water deficit and, 1019
  - dehydration, 1034
- Hyperoxaluria, 366*t*
- Hyperparathyroid myopathy, 279, 1077–1078
- Hyperparathyroidism, 258, 263, 279, 337, 535*t*, 1040, 1043, 1077–1078, 1077*t*, 1082, 1089–1090
  - secondary, 256
- Hyperperfusion injury to the cerebrum, 50
- Hyperpnea, 8
- Hyperprolactinemia, 330–331, 331*t*
- Hypersomnias
  - idiopathic, 923
  - Kleine–Levin syndrome, 923–924
  - narcolepsy. *See* Narcolepsy
- Hypertension, 101
  - acute, 101–102
    - vasoconstriction in, 102
  - angiotensin-converting enzyme inhibitors for, 103
  - antihypertensive medications for, 104–105
  - aortic arch atherosclerosis, 118
  - bevacizumab and, 528
  - calcineurin inhibitors and, 797
  - cardiac embolus risks, 118–119
  - carotid artery stenosis risks, 115–117
  - cerebral aneurysms associated with, 106–107
    - subarachnoid hemorrhage, 107–108
    - unruptured cerebral aneurysms, 106–107
  - cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), 115
  - cerebral ischemia and, 104–105
  - chronic, 101–102
    - cerebral vascular remodeling caused by, 102
  - definition of, 101
  - dementia risks, 118–119
  - in eclampsia, 121
  - epidemiology of, 101–102
  - evaluation of, 103
  - and headache, 1049–1050

Hypertension (*Continued*)
  immunosuppression, 121
  and intracerebral hemorrhage, 1092
  intracerebral hemorrhage risks, 108–111
  intracranial atherosclerosis risks, 117–118
  lacunar infarct risks, 111–114
  lifestyle modifications for, 103
  and migraine, 1048–1050
  pathophysiology of, 102–103
  periventricular white matter disease risks, 114–115, 114*f*
  pharmacologic treatment of, 104–105
  stroke risks, 103–105, 104*t*, 172
    in patients with chronic kidney disease, 259
  thoracic aortic aneurysms and, 37–38
  treatment of, 103
Hypertensive disorders of pregnancy, 584
Hypertensive encephalopathy, 101–102, 119–121, 120*f*. *See also* Posterior reversible encephalopathy syndrome (PRES)
  calcineurin inhibitors and, 797
  causes of, 101, 119
  diagnostic imaging of, 119–121
  dialysis and, 260–261
  eclampsia, 121, 599
  lupus and, 888
  metabolic encephalopathy and, 1089
  signs and symptoms of, 119
  treatment of, 119–121
  uremic encephalopathy and, 252, 1008
  vasogenic cerebral edema and, 119–121
Hyperthermia, 665, 667–669
  cardiovascular manifestations of, 668
  causes of, 662*t*
  cooling methods for, 668–669
  dehydration and, 665
  drugs that cause, 666*t*
  environmental causes of, 665
  hypotension caused by, 669
  malignant, 624, 662*t*, 664, 666*t*, 668, 967, 973, 980*t*, 985, 987–988, 1002, 1077*t*
  management of, 666*t*, 668–669
  neurologic conditions associated with, 662
  neurologic manifestations of, 667–668
  non-neurologic causes of, 668
  patient management, 668–669
  periodic, 664
  respiratory alkalosis caused by, 668
  systemic manifestations, 668
Hyperthyroidism
  atrial fibrillation and, 299
  causes of, 291–292
  and migraine, 1047, 1051
  neurologic complications of
    chorea, 296, 1031
    corticospinal tract dysfunction, 295
    encephalopathy, 298
    Hashimoto encephalopathy, 299–301
    mental disorders, 299
    mononeuropathies, 295
    movement disorders, 296
    myasthenia gravis, 295
    myopathy, 292–293, 1077–1078
    periodic paralysis, 293–294
    peripheral neuropathy, 295
    psychiatric disorders, 299
    seizures, 299
    stroke, 299
    thyroid storm, 298
    thyroid-associated ophthalmopathy, 296–298, 297*f*
    tremor, 296
  skeletal muscle affected by, 292–293, 1083–1084
Hypertrophic cardiomyopathy, 74, 81, 124
Hypertropia, 424, 428
Hyperventilation. *See also* Hyperpnea
  central neurogenic, 9
  syncope and, 133
Hyperviscosity, 59, 182, 449–451, 500*t*, 1031
Hypnagogic hallucinations, 921
Hypnic headache, 1054
Hypnotics, 619
  for jet lag disorder, 930
  peripheral neuropathy and, 619
Hypoactive delirium, 967–968
Hypoactive sexual desire disorder (HSDD), 563
Hypoacusis, 984–985
Hypoadrenalism, 336, 663*t*, 665
Hypocalcemia
  chorea and, 591, 1031
  description of, 278–279, 338, 380–381, 1031
  neuromuscular signs, 997, 1005
  seizures, 60–61, 971, 1019
Hypocapnia, 18
  central sleep apnea, 17
Hypocholesterolemia, familial, 209
Hypocretin
  description of, 915
  narcolepsy and, 921
Hypogastric plexus, 561–562
Hypoglossal nerve stimulator, 927
Hypoglycemia, 45, 48, 60, 68, 132, 262, 287, 500*t*, 582, 628, 663*t*, 665, 668, 670, 794, 813*t*, 824, 981, 1010, 1064*t*, 1073, 1089, 1095
  chorea and, 1031
  definition of, 304
  diabetes mellitus and, 304
  migraine and, 1053*t*
  seizures and, 1017, 1019
  tremor and, 1040
Hypoglycemic encephalopathy, 1089, 1095
Hypoglycorrhachia, 812, 824, 872–873
Hypokalemia, 103, 167, 277–278, 623, 1082
Hypokalemic alkalosis, 338
Hypokalemic periodic paralysis, 293, 624, 1058*t*, 1082
Hypomagnesemia, 167, 280, 1019–1020, 1051
Hypomelanosis of Ito, 361
Hyponatremia, 273–276, 278, 785
  brain edema and, 199
  central pontine myelinolysis and, 275–276, 276*f*, 633
  chronic, 275–276
  effective blood volume reductions caused by, 125
  encephalopathy caused by, 274
  in hospitalized patients, 274
  hyperosmolarity and, 274
  hypo-osmolar, 274
  MDMA (ecstasy) ingestion and, 640
  neurologic symptoms related to, 274
  subarachnoid hemorrhage and, 274–275
  syndrome of inappropriate antidiuretic hormone and, 273, 526
  treatment of, 275, 633
Hypo-osmolar hyponatremia, 274
Hypoparathyroidism, 278, 338, 1031
Hypoperfusion, stroke due to, 44
Hypophosphatemia, 634

Hypophosphatemic osteomalacia, 381, 500*t*
Hypophyseal-portal system, 328
Hypopituitarism, 336–337, 337*t*
Hypoplastic left heart syndrome (HLHS), children with, 53–55, 61–62
Hypopnea
  definition of, 925
  polysomnography of, 925–926, 926*f*
Hypotension
  and brain injury, 56
  hyperthermia and, 669
  intracranial
    headache and, 970
  intradialytic, 261
  postural. *See* Postural hypotension
Hypothalamic hypogonadism, 301
Hypothalamic lesions, 662–663
Hypothalamopituitary disorders, 328, 330–336, 334*t*, 336*t*, 339, 339*t*
  amenorrhea and, 567
  sexual dysfunction and, 567–568
Hypothalamus
  autonomic regulation, cardiovascular, 126, 244
  disorders of, in sarcoidosis, 352*t*, 869–870
  dysfunction of, 207, 207*t*, 279, 286, 434, 448, 508, 629–630
  hormones produced by, 330*t*. *See also individual hormones and diseases*
  Horner syndrome, 435
  paraneoplastic disorders of, 502*t*, 508, 510–511
  paraventricular nucleus of, 158
  radiation and, 535*t*
  respiration and, 10
  reticular activating system and, 1086, 1087*f*, 1089–1090
  suprachiasmatic nucleus of, 914, 936
  and temperature regulation, 661–665, 667*t*
  and thyroid disease, 286, 301
Hypothermia, 665
  accidental, 665
  during cardiac bypass for surgery, 47–48
  causes of, 663*t*
  in diabetes, 663
  drugs that cause, 667*t*
  dysarthria caused by, 669
  electrolyte disturbances from treatment of, 671
  electrolytes affected by, 670
  environmental causes of, 665
  hypothalamic pathology and, 670
  intubation for, 670
  laboratory tests, 670
  management of, 670–671
  metabolic derangements and, 670
  myotonia and, 669
  neurologic conditions associated with, 662
  neurologic manifestations, 669
  patient management, 670–671
  prognosis for, 671
  pupillary reaction to light in, 669
  renal manifestations of, 670
  rewarming methods for, 670
  shivering phase of, 669–670
  spinal cord pathology and, 670
  systemic manifestations, 669–670
  therapeutic, 671
  topical hypothermia
    internal thoracic artery dissection and, 46
Hypothyroidism
  anticonvulsant therapy, 291, 1019
  carpal tunnel syndrome and, 291, 1068
  cerebellar ataxia and, 289
  cognitive dysfunction and, 1103
  coma and, 287–288
  congenital, 286
  cranial nerve disorders and, 289–291
  diffuse peripheral neuropathy and, 291
  dysphonia in, 289
  encephalopathy and, 287–288
  entrapment neuropathy and, 291, 1064–1065, 1068
  etiology of, 286
  giant cell arteritis and, 291
  Hashimoto thyroiditis and, 299–300, 1031
  incidence of, 286
  mental changes and, 288
  and migraine, 1047, 1051
  myasthenia gravis and, 291
  myopathy, 289–291, 1077–1078, 1077*t*
  myxedema coma and, 287
  neurologic complications of, 286, 1078
  and parkinsonism, 1043
  peripheral neuropathies and, 291, 1064*t*
  polymyalgia rheumatica and, 291
  sarcoidosis and, 873–874, 883
  seizures and, 287–288, 1019
  Sjogren syndrome, 890
  sleep disorders and, 288, 925
  subclinical, 291
  symptoms of, 287
  systemic sclerosis and, 893
Hypoxemia and brain injury, 56
Hypoxia-ischemic disorders
  chorea and, 1024–1025
  dystonia and, 1024–1025
  global hypoxia-ischemia, 1033–1034
  myoclonus and, 1033–1034
  stroke, 1024, 1033
Hypoxia-ischemic encephalopathy, 18, 49, 147–148, 151, 153, 1089, 1094–1095, 1098
Hysteria. *See* Functional neurologic disorders (FNDs)

I

Idarucizumab, 79, 468
Idiopathic hypersomnias, 916, 922*t*, 923
Idiopathic intracranial hypertension, 422–423, 423*f*, 442, 457, 604, 711
  in pregnancy, 583–588
Ifosfamide, 243*t*, 336*t*, 522*t*, 523*t*, 526, 606, 1036*t*, 1039*t*
IgA myeloma, 449
IgG4-related disease, 849–850
  diagnostic testing, 849–850
  presentation, 849
  risk factors, 849
  treatment, 850
Iglon5, 16, 502, 506
IgM monoclonal gammopathy, 1041
IL6 receptor, 420–421
Imaging procedures
  angiography. *See* Angiography
  computed tomography. *See* Computed tomography
  contrast material
    iodinated, 951–952
    neurologic complications of, 951–953
  discography, 958

Imaging procedures (*Continued*)
  magnetic resonance imaging. *See* Magnetic resonance imaging (MRI)
  myelography. *See* Myelography
  pulmonary function evaluations, 7
Imerslund–Graesbeck syndrome, 444
Imipenem, 94, 605*t*, 606, 611, 620, 620*t*, 788, 1021, 1036*t*
Immune brachial plexopathy, 1061
Immune checkpoint inhibitors (ICIs), 459–460, 481, 522*t*, 529, 617*t*, 620, 620*t*, 621*t*, 622, 757, 780, 789, 800–801, 1064*t*, 1075*t*
Immune effector cell-associated neurologic syndrome, 529
Immune effector cell-associated neurotoxicity syndrome, 459, 801
Immune reconstitution inflammatory syndrome (IRIS), 720, 724, 739, 758*t*, 771–772, 775, 779–780, 782, 789–790, 806–807, 814, 817, 842–843, 845
Immune thrombocytopenia, drug-induced, 462
Immune-mediated disease
  otoneurologic manifestations of, 407–408
  sarcoidosis, 407
Immune-mediated hypersensitivity syndrome, 1011
Immune-mediated neuropathies
  chronic inflammatory demyelinating polyradiculoneuropathy. *See* Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
  Guillain–Barré syndrome. *See* Guillain–Barré syndrome
  multifocal, 1067
Immune-related adverse events (irAEs), 800
Immunizations. *See* Vaccine(s)
Immunocompromised patients, viral encephalitis in, 757
Immunodeficiency. *See also* AIDS; Human immunodeficiency virus
  in myelomatosis, 451
  neurologic complications of, 451
Immunomodulatory therapies, complications of, 529–530, 797–801
  azathioprine, 799
  calcineurin inhibitors, 797
  chimeric antigen receptor (CAR) T-cell therapy, 529–530, 801
  corticosteroids, 798–799
  disease-modifying therapies (DMT) for multiple sclerosis, 800
  immune checkpoint inhibitors (ICIs), 800–801
  mycophenolate mofetil (MMF), 799–800
  OKT3 monoclonal antibody, 799
  rapamycin inhibitors, mammalian target of, 797–798
  sarcoidosis, 882–883
Immunosuppression. *See also individual disorders*
  for acute disseminated encephalomyelitis, 763
  calcineurin inhibitors. *See* Calcineurin inhibitors
  corticosteroids as. *See* Corticosteroids
  gestational, 324
  infection risks, 787
  after liver transplantation, 795
  lymphoproliferative disorders and, 790–791
  for neurosarcoidosis, 883–884
  for paraneoplastic cerebellar degeneration, 512
  sarcoidosis, 882–883
  seizures and, 1017
  strongyloidiasis in, 834
  for systemic lupus erythematosus, 889–890
  tremor and, 1039*t*
Inactivated vaccines, 854
Inborn errors of folate absorption, 239
Inclusion-body myopathy, Paget disease, and frontotemporal dementia, 386–387
Inclusion-body myositis/myopathy, 503*t*, 520, 782, 1077*t*, 1080–1081
Incomitant misalignment, 424–425
Incontinentia pigmenti, 360–361, 361*f*
Infantile beriberi, 244
Infantile neuroaxonal dystrophy, 383
Infantile nystagmus syndrome, 432–433
Infantile vitamin B_{12} deficiency, 444
Infant(s). *See also* Neonates
  bacterial meningitis in, 692, 696
  botulism in, 1074
  brain abscess in, 693
  brain injury in premature infants, 56
  sudden infant death syndrome, 17
Infections
  central nervous system. *See* Central nervous system (CNS) infections
  cerebral. *See* Cerebral infection
  fungal. *See* Fungal infections
  Guillain–Barré syndrome and. *See* Guillain–Barré syndrome
  headache and, 1050
  immunosuppression and, 787
  intravenous drug abuse as cause of, 645
  leukemia and, 449
  movement disorders caused by, 1028–1030, 1029*t*
  myopathies caused by, 1078–1079
  otoneurologic manifestations of, 405–407
  parkinsonism and, 1045
  in pregnancy, 588–590
  tremor and, 1040
Infective endocarditis (IE), 58, 76–77, 87, 1091–1092. *See also* Endocarditis
  left-sided, 91, 93
  neurologic complications of
    brain imaging, 94–95
    cerebral infection, 98
    cerebrospinal fluid (CSF) examination, 95
    clinical presentation, 93–94
    echocardiography, 95
    embolization as cause of, 89*f*, 91
    epidemiology of, 87–88
    evaluation of patients, 94–95
    extracerebral neurologic complications, 98
    hemorrhagic stroke, treatment of, 93–94, 97
      intraparenchymal hemorrhage, 97
      mycotic aneurysms, 97
    intracerebral hemorrhage, 92–95, 97
    ischemic stroke, 92–95
      antibiotic therapy, 95
      anticoagulant therapy, 96
      antiplatelet therapy, 95–96
      description of, 92–93
      intracerebral hemorrhage secondary to, 93
      surgical treatment, 96
      thrombolysis, 95–96
      treatment of, 95–96
    management algorithms for, 98
    meningitis, 91, 97
    mortality rates, 99
    mycotic aneurysms, 88, 89*f*, 91*f*, 92*t*, 93–94, 97, 99*f*
    neurologic complications of, 88–91
    pathophysiology of, 88–91
    prognosis, 98–99
    risk factors for, 91–92, 91*t*
    seizures, 94–95
    vascular imaging, 94–95
  with secondary embolism, 59–60
  site of infection, 91

Inferior hypophyseal artery, 328
Inflammatory bowel disease, 204–207, 205*t*, 1016. *See also* Crohn disease; Ulcerative colitis
  cerebrovascular disease and, 206
  demyelinating disease and, 206
  myelopathy and, 206
  myopathy, 206
  peripheral neuropathy and, 205–206
Inflammatory demyelinating optic neuritis, 417–418, 418*f*
  residual deficits, 417
Inflammatory myopathies. *See also individual disorders*
  drug-induced, 621–622
  respiratory dysfunction and, 15
Inflammatory polyneuropathies. *See also individual disorders*
  HIV and, 781–782
Infliximab, 391, 394, 604, 615, 617*t*, 618, 738, 848, 882, 892, 897
Influenza
  in children, 862
  definition of, 862
  vaccine for, 862–863
Inhibitory Control Test (ICT), 195
Innominate artery
  anatomy of, 28, 33*f*
  blockage of, 29–30
Insecticides, 658–659
Insomnia, 60
  assessment of, 917–918
  classification systems for, 916–917
  clinical assessment of, 917–918
  comorbidities, 917, 917*t*
  consequences of, 917
  definition of, 916–917
  diagnosis of, 917–918
  headache and, 937
  hyperarousal and, 918
  medications associated with, 917*t*
  morbidity and mortality associated with, 915
  pathophysiology of, 918
  primary, 917
  risk factors for, 917
  secondary, 917
  substances associated with, 917*t*
  3P model of, 918
  treatment of, 918–920
    antidepressants, 920
    antiepileptic drugs, 920
    atypical antipsychotics, 920
    benzodiazepine receptor agonists, 918, 919*t*
    cognitive behavioral therapy, 918, 919*t*
    melatonin receptor agonists, 919–920
    pharmacologic, 918, 919*t*
Insomnia Severity Index, 917–918
Insular cortex, 159
Insular stroke, 160
Insulin, 45, 125, 252, 263, 278, 287, 294, 298, 304, 308, 311, 331, 340, 357*t*, 607, 614, 623, 796, 883, 1019
Insulin resistance, 158, 184, 320, 773–774, 1001, 1082
Insulin resistance and Alzheimer disease, 314
Intensive care, acute necrotizing myopathy of, 997*t*, 998*t*, 1002, 1005
Intensive care unit (ICU), 14, 44, 97, 128, 165, 167–168, 278, 287, 623, 637, 810, 860–861, 966, 971, 973, 988, 999*t*, 1035, 1069, 1090, 1094, 1116
  anesthetic drugs in, 988
  sedation in, 988
Intention tremor, 113, 447, 658, 1038–1041, 1039*t*
Intercostal neuropathies, 309–310
Interferon-α, 619
Interferon-γ, 728
Interictal phenomena, 566
Interleukins, 324, 390, 458, 496, 522*t*, 523*t*, 606, 608, 690, 729, 780, 801, 849, 869*f*, 894, 994, 1048*t*, 1087*f*
Intermittent claudication
  coarctation of the aorta and, 38–39
  definition of, 28
  spinal cord ischemia secondary to, 28
Internal carotid artery stenosis, 115–116
Internuclear ophthalmoplegia, 207, 279, 425–426, 426*t*, 429–430, 443, 545, 615
Interstitial cells of Cajal, 218, 229
Interstitial lung disease, 1079–1080
Intervertebral disc
  acute prolapse of, in pregnancy, 594–595
  description of, 373
  disease of, 374–376
Intoxication
  alcohol, 70, 356, 357*t*, 622, 627, 630
  arsenic, 654
  cocaine, 638
  dextromethorphan, 643–644
  gamma hydroxybutyrate, 640–641
  hallucinogens, 643
  heavy metals, 131, 516
  ketamine, 643
  lithium, 611
  marijuana, 644–645
  MDMA (ecstasy), 640
  methamphetamine, 638
  nitrous oxide, 644
  opiate, 641–643
  phencyclidine, 643
  sedative-hypnotics, 607, 630, 641
  thallium, 367*t*
Intra-aortic balloon pump, 49
Intracerebral hemorrhage (ICH), 96, 157–158, 605. *See also* Intracranial hemorrhage
  amphetamine and, 108
  brain tumors and, 108
  after CABG, 44
  cavernous malformation with, 108, 110*f*
  clinical presentation of, 94, 109, 110*t*
  cocaine and, 108
  computed tomography of, 109–110
  and extracorporeal membrane oxygenation (ECMO), 48–49
  hypertension as risk factor for, 108–111
  infective endocarditis and, 88, 90*f*, 92*t*, 93–94, 97
  ischemic stroke as cause of, 92–93, 108
  magnetic resonance imaging of, 109–110
  methamphetamine abuse and, 639*f*
  primary hypertensive, 109
  prognosis for, 109
  risk factors for, 108
  septic emboli as cause of, 88
  and stroke, 182
  supratentorial, 111
  surgical evacuation of, 111
  treatment of, 97, 111
Intracranial bleeding, in hemophilia A, 460
Intracranial hemorrhage, 59, 78–79, 94. *See also* Intracerebral hemorrhage (ICH)
  drugs that cause, 605
  hematologic disorders and, 448–449

Intracranial hemorrhage (*Continued*)
  myelography and, 957
  stroke caused by, 108
  in thrombocytopenia, 448–449, 463
Intracranial hypertension
  acute encephalopathy associated with, 530
  in acute liver failure, 196, 794, 1090
  in Behçet disease, 906
  brain tumors and, 265, 456, 476–477, 530, 582
  in cerebral malaria, 829–830
  in cryptococcal meningitis, 779, 789, 816–817, 842
  description of, 327, 422, 423*t*
  in dialysis dysequilibrium syndrome, 262
  dural arteriovenous fistula and, 587
  hiccup and, 10
  hypercapnia and, 18
  hypoxic encephalopathy and, 148
  idiopathic, 422–423, 422*f*, 423*f*, 583, 604, 711
Intracranial hypotension, 491, 841*t*, 970, 971*f*, 986, 1051
Intracranial tuberculoma, 725, 844
Intracranial tumors, in pregnancy, 582
Intradialytic hypotension, 261
Intramedullary arteriovenous malformations, 962
Intraoperative transesophageal echocardiography, 47
Intraparenchymal hemorrhage. *See also* Intracerebral hemorrhage (ICH); Intracranial hemorrhage
  in patients with infective endocarditis, 97
Intrathecal chemotherapy, 530, 684, 688, 688*t*, 841*t*, 850, 1059
Intravascular lymphoma, 454–455, 454*f*, 455*f*, 495
Intravenous immunoglobulin (IVIg), 761, 763, 889–890
  for acute disseminated encephalomyelitis, 763
  aseptic meningitis and, 523*t*, 604, 748, 798*t*, 840*t*, 850
  for celiac disease, ataxia of, 204
  cerebral malaria and, 824
  for chronic inflammatory demyelinating neuropathy, 507
  for critical illness polyneuropathy, 1001
  for Guillain–Barre syndrome, 128, 597, 781, 1070
  headache from, 604
  for inflammatory myositis, 519, 1080–1081
  for MGUS neuropathy, 1070
  for Miller Fisher syndrome, 429
  for multifocal motor neuropathy, 291, 597, 1067
  for multiple sclerosis, 324
  for myasthenia gravis, 597, 973–974, 988, 1075–1076
  for neuromyotonia, 519
  for paraneoplastic disorders, 506*t*, 512, 1060, 1075
  plasmapheresis and, 1070
  for plexopathy, 1061
  for relapsing polychondritis, 394
  for small-fiber neuropathy, 882
  for stiff person syndrome, 515
  for Sydenham chorea, 1028
  for West Nile virus encephalitis, 755
Intravesical pressure, 553
Involuntary respiratory control, disorders of, 9
  acquired central hypoventilation, 9
  congenital central hypoventilation syndrome, 9
Iodinated contrast, 577–578, 952
Ionizing radiation, 951–953
Iophendylate, 958
Ipilimumab, 460, 481, 482*t*, 523*t*, 529, 622
Iron-deficiency anemia, 206, 442, 932*t*
Irregular breathing. *See* Ataxic breathing
Irregular sleep-wake disorder, 930, 936
Ischemic cardiomyopathy, 74, 83
Ischemic complications following CABG, 44–45, 50
Ischemic injury, nerve biopsies, 1061
Ischemic monomelic neuropathy, 32–33, 261–262
Ischemic neuropathy
  dialysis and, 261–262
  focal, 1063–1065
Ischemic oculomotor palsies, 428
Ischemic optic neuropathy, 44–45, 259, 419–421, 420*t*
Ischemic spinal cord syndromes, 24–28
  anterior spinal artery syndrome, 27
  intermittent claudication, 28
  motor neuron disease, 27
  posterior spinal artery syndrome, 27–28
  unilateral cord syndromes, 28
Ischemic stroke, 50, 65–67, 80, 87–88, 93–95, 171–172, 179. *See also* Stroke
  after cardiac surgery, 44
  alcohol and, 635
  alcoholism as risk factor for, 184, 184*f*
  antibiotic therapy, 95
  anticoagulation, 96
    in native valve endocarditis, 96
    in prosthetic valve endocarditis, 96
  antiphospholipid antibodies in, 470–471
  antiplatelet therapy, 95–96
  aspirin prophylaxis, 114, 116–117
  atrial fibrillation after, 164
  autonomic dysfunction after, 165
  cardiac disease among patients of, 164
  cardiac troponin, rise in, 162–163
  clinical presentation, 93–94
  coronary artery disease (CAD) in patients with, 159–160, 166–167
  cutaneous manifestations of, 348*t*
  description of, 92–93
  embolic ischemic strokes, 166
  hemorrhagic transformation of, 94
  human immunodeficiency virus (HIV) and, 773
  intracerebral hemorrhage secondary to, 108
  lacunar infarct as cause of, 111–114
  methamphetamine and, 639
  neurosarcoidosis as cause of, 875
  oral contraceptives and, 319–320
  patients, evaluation of, 94–95
    brain imaging, 94–95
    cerebrospinal fluid (CSF) examination, 95
    echocardiography, 95
    vascular imaging, 94–95
  for patients on ECMO, 49
  in pregnancy, 174–175, 584
  renal disease and, 258–259
  seizures secondary to, 94–95
  surgical treatment, 96
  systemic lupus erythematosus and, 888–889
  thrombolysis, 95–96
  and tuberculous meningitis, 180
  watershed infarction as cause of, 44
Ischemic stroke, cardiac causes of, 69–77
  endocarditis, 76–77
    infective endocarditis, 76–77
    marantic (nonbacterial thrombotic) endocarditis, 77
  left atrium, 69–73
    atrial fibrillation and flutter, 69–72
      cardioversion, 72
      pathophysiology, 70
      risk stratification, 70–72
    atrial myxoma, 73

    chronic sinoatrial disorder, 72–73
  left ventricle, 74–75
    acute myocardial infarction, 74
    cardiomyopathies, 74–75
    left ventricular dysfunction, 75
  paradoxical embolus, 73
  valvular diseases, 75–76
    aortic valve stenosis, 76
    lambl excrescences, 76
    mitral annular calcification, 75
    mitral valve prolapse, 75
    mitral valve regurgitation, 75
    mitral valve stenosis and rheumatic heart disease, 76
    prosthetic heart valves, 76
Isoflurane, 987
Isoniazid, 253, 306*t*, 605–606, 608, 614, 1034, 1036
  mixed sensorimotor neuropathy caused by, 617*t*, 618, 1064, 1072
  optic neuropathy and, 614
  seizures caused by, 605–606, 605*t*, 1014*t*, 1021
  for tuberculous meningitis, 723–725, 780
Itraconazole, 618
Ivermectin treatment, of onchocerciasis, 836
Ixabepilone, 522*t*, 523*t*, 525–526, 617, 617*t*
Ixazomib, 617
Ixodes ticks, 707–708, 708*f*

J

JAK2 mutation, 455, 457
Janeway lesions, 350
Japanese encephalitis virus, 687, 742, 743*t*
JC virus (JCV), 267, 606, 741–742, 744*t*, 749, 776*t*, 780, 788*t*, 789, 847, 1037, 1044
Jerk nystagmus, 431
Jeryl Lynn vaccine, 860
Jet lag disorder, 914, 930, 930*f*
Joubert syndrome, 12, 270
J-point elevation, 670
Jugular foramen syndrome, 483*t*

K

Kanzaki disease, 366*t*
Kappa beta (κß) system, 993
Karnofsky performance status, 478–479
Kayser–Fleischer rings, 212, 212*f*
Kearns–Sayre syndrome, 279, 338
Kennedy syndrome, 327, 571, 1058
Kernicterus, 446
Kernig sign, 684–685
Ketamine, 643, 989
Ketoconazole, for coccidioidal meningitis, 818
Ketolides, 619
Kidney(s). *See also specific renal entries*
  disease of. *See* Dialysis; Dialysis disequilibrium syndrome; Renal disease; Renal transplantation; Uremic encephalopathy; *specific entries*
  hereditary disorders of, 270
    Fabry disease, 127, 267, 347–349, 348*t*, 366*t*, 1063*t*, 1073
    von Hippel–Lindau disease, 269, 270*f*
  polycystic kidney disease, 269–270
  transplantation of, 264, 795
Kienback sign, 13–14
Kir2.6, 294
Kleine–Levin syndrome, 922*t*, 923–924
Klüver–Bucy syndrome, 565
Kocher–Debré–Sémélaigne syndrome, 289
Kölliker-Fuse nuclei, 4
Kölliker-Fuse–parabrachial complex, 8
Konzo, 248
Korsakoff syndrome, 244, 596, 628*f*, 630–631, 786
  behavioral deficits in, 631
  diagnosis of, 631
  hyperemesis gravidarum complicated by, 596
  thiamine deficiency and, 244
  Wernicke encephalopathy and, 244, 357*t*, 631

L

La Crosse virus, 687, 743*t*
Labyrinthine disorders, 400–401
Lacosamide, 315, 321, 579, 587, 971, 1009*t*, 1010*t*, 1012, 1019
Lactation
  acetaminophen during, 582
  statin drugs during, 584–585
Lactulose, 145, 197–199
Lacunar infarct, 111–114
  carotid artery stenosis and, 111–112
  characteristics of, 111, 112*f*
  clinical syndrome of, 113
  diabetes mellitus and, 111
  discovery of, 111
  etiology of, 112–113
  hypertension as risk factor for, 111
  magnetic resonance imaging of, 114*f*
  sites of, 111, 113
  treatment of, 113–114
Lacunar syndromes
  ataxic hemiparesis, 113
  clinical presentation of, 113
  diagnostic imaging of, 113
  pure motor hemiparesis, 113
  sensorimotor syndrome, 113
  tissue plasminogen activator for, 113
LAMB2 gene, 260
Lambert–Eaton myasthenic syndrome (LEMS), 12*t*, 15, 499–501, 501*t*, 504*t*, 506*t*, 517–519, 997, 997*t*, 1075–1076
Lambl excrescences, 76
Lamotrigine, 255, 315, 321, 495, 519, 566, 572*t*, 578–581, 609, 615, 781, 840*t*, 850, 924, 1009*t*, 1010*t*, 1011, 1016–1017, 1027*t*, 1036*t*, 1039*t*, 1068
Lance–Adams syndrome, 1033–1034
Large B-cell lymphoma, 455, 495
Large-fiber peripheral neuropathy, 875–876
Laryngeal nerve palsy, recurrent, 301
Laryngospasm, 609, 952, 1031
L-asparaginase, 177, 182, 522*t*, 606, 1018
Late delayed radiation myelopathy, 533–534
Late delayed radiation plexopathy, 534–535
Latent nystagmus, 433
Lateral femoral cutaneous neuropathy, 202
Later-onset cognitive decline after CABG, 46
Lathyrism, 247–248
Lathyrus sativus, 247
Lead, 652–654, 1036*t*, 1039*t*, 1064*t*, 1073
  encephalopathy caused by, 653
  neuropathy from, 654–655
  occupational exposure to, 653
Leber hereditary optic neuropathy (LHON), 416*t*, 421–422
Leeuwenhoek disease. *See* Diaphragm myoclonus
Left atrial appendage (LAA), 70–72, 72*f*
Left atrial substrate, aberrant, 70

- Left atrium, 69–73, 173
  - atrial fibrillation and flutter, 69–72
    - cardioversion, 72
    - pathophysiology, 70
    - risk stratification, 70–72
  - atrial myxoma, 73
  - sinoatrial disorder, chronic, 72–73
- Left recurrent laryngeal nerve, 31
- Left ventricle, 74–75
  - acute myocardial infarction, 74
  - cardiomyopathies, 74–75
- Left ventricular dysfunction, 75, 80
  - after subarachnoid hemorrhage, 162
- Left ventricular ejection fraction, 75
- Left-sided obstructive cardiac lesions, 54
- *Legionella pneumophila*, 1030
- Legionnaire disease, 1030
- Lemborexant, 919*t*, 920
- Lenalidomide, 522*t*, 523*t*, 617
- Lennox–Gastaut syndrome, 606, 859, 1011
- Leprosy, 727–740, 1068
  - autonomic neuropathy in, 732
  - bacterial factors, 729–730
  - borderline, 731, 732*f*
  - clinical manifestations, 730–732
  - clofazimine for, 735, 738
  - cutaneous manifestations of, 366*t*
  - diagnostic studies, 732–734
    - electrodiagnostic studies, 732–733
    - nerve biopsy and pathology, 733–734
    - ultrasonography, 733
  - discovery of, 365
  - drug resistance and, 735–736
  - epidemiology, 728
  - erythema nodosum leprosum (ENL), 736–737
  - genetic susceptibility to, 729
  - host factors, 728–729
  - and human immunodeficiency virus infection, 738–739
  - incidence of, 728
  - lepromatous, 365–367, 367*f*, 730–731, 732*f*, 734, 737–738
  - manifestations of, 730–732
  - multidrug therapy (MDT) for, 734–736
  - *Mycobacterium leprae*, 727
  - pain in, 732
  - pathology, 733–734
  - peripheral neuropathy in, 365, 735
  - prevention, 739–740
  - primary neuritic, 732
  - reactions associated with, 736–737
  - transmission of, 728
  - treatment, 734–736
  - tuberculoid, 731, 731*f*
  - type 1 lepra reactions, 736–737
  - type 2 lepra reactions, 737–738
- Leptin, 378
- Leptomeningeal carcinomatosis, 490, 850
- Leptomeningeal metastases
  - clinical features of, 490
  - definition of, 490
  - diagnostic studies of, 491–492, 491*f*
  - epidemiology of, 490
  - pathophysiology of, 490
  - prognosis for, 492–493
  - treatment of, 492, 530
- Leptospirosis, 352*t*, 703, 812*t*, 840*t*
- LepVax, 739
- Letterer–Siwe disease, 357*t*
- Leukemia, 447–449
  - acute myelomonocytic, 448–449
  - cellular hyperviscosity, 449
  - chloromas, 448
  - infections and, 449
  - intracranial hemorrhage, 448–449
  - localized deposits, 448, 448*f*
  - meningeal, 447–448
  - neurocutaneous manifestations of, 352*t*
  - promyelocytic acute myeloid, 464*f*
- Leukoaraiosis, 114–115, 544
- Leukoencephalopathy, 115, 606, 638
  - chemotherapy and, 524, 524*f*, 530, 606
  - with cutaneous lesions, 349, 362*t*
  - diabetic, 303, 313–314, 313*f*
  - methotrexate and, 524, 524*f*, 530, 606
  - posterior, 254–255
  - progressive multifocal, 267, 269*f*, 451, 500*t*, 523, 606, 741, 757–758, 758*f*, 772, 776*t*, 780, 789, 789*f*
  - radiation and, 531, 533
  - toxic, 642
- Levetiracetam, 255, 321, 479, 572*t*, 578–580, 609–610, 759, 787, 936, 971, 1009*t*, 1010–1012, 1010*t*, 1017–1019, 1033–1034, 1037–1038
- Levodopa, 11, 125, 226, 258, 442–443, 567, 572*t*, 591–592, 606–611, 613, 615–616, 617*t*, 619, 622, 656, 931–933, 932*t*, 965–966, 987, 1025–1028, 1027*t*, 1033, 1035, 1036*t*, 1041–1045, 1048*t*
  - in dopamine-responsive dystonia, 1033
  - dystonia and, 1033
  - half-life of, 965–966
  - halothane avoidance with, 966
- Levodopa-induced dyskinesias, 610
- Levofloxacin, 724, 736*t*
- Lewis–Sumner syndrome, 1067
- Lewy bodies, 1011
- Lewy body disease, 127, 226, 424, 547, 969
- Lewy neurites, 226
- Lhermitte phenomenon, 443, 486, 528
- Lhermitte sign, 374, 527, 531*t*, 533, 616
- Libido, 558
- Libman–Sacks endocarditis, 180–181
- Light chain deposition disease, 451–452
- Lightning strikes, 411
- Limb-girdle muscular dystrophy, calpainopathy, 457
- Limb-girdle syndromes, 15
- Limbic encephalitis, 274, 393–394, 460, 501*t*, 502*t*, 506*t*, 507–508, 1015
- Lincomycin, 615, 620
- Linear sebaceous nevus syndrome, 361–362, 361*f*, 366*t*
- Lipopolysaccharide, 690, 994–995, 1069
- *Listeria monocytogenes*, 266–267, 590, 787, 788*t*, 791, 793
  - meningitis, 266, 684, 689*t*, 690
  - in pregnancy, 590
- Listeriosis, 352*t*
- Lithium
  - headache and, 1051, 1053*t*
  - HIV and, 769
  - hypothermia and, 667*t*
  - Kleine-Levin syndrome and, 924
  - movement disorders and, 609–611, 932*t*, 1026, 1027*t*, 1033, 1035, 1036*t*
  - neuroleptic malignant syndrome and, 612–613
  - neuromuscular transmission disorders and, 1075
  - neuropathy and, 617*t*, 619

  nystagmus and, 615
  parasomnias and, 933, 935
  seizures induced by, 605–607, 1021
  toxicity caused by, 1035
  tremor induced by, 611, 1038–1039
Livedo reticularis, 351
Liver disease and headache, 1052
Liver failure. *See also* Hepatic disorders
  acute
    hepatic encephalopathy in, 193, 196, 199
  cerebral edema in, 1089–1090
  metabolic encephalopathy caused by, 1089–1090
  Wilson disease and, 211, 214
Liver transplantation, immunosuppression after, 795
Loa loa, 836
Local anesthetics, 971
Locked-in syndrome, 9–11, 633, 1092–1093, 1119
Loiasis, 836
Long QT syndrome (LQTS), 83
Loop diuretics, ototoxicity caused by, 411, 614
Lorazepam, 934*t*, 989
L-ornithine-L-aspartate (LOLA), 198
Louis-Bar syndrome. *See* Ataxia-telangiectasia
Low-density lipoprotein (LDL), 172
Lowe syndrome, 270
Lower urinary tract
  function of, 541
  innervation of, 542, 543*f*
  neurotransmitters and, 542–544, 543*f*
Lower urinary tract dysfunction
  description of, 541
  diagnostic evaluation of
    bladder diary, 548, 549*f*
    bladder scan, 549
    cystometry, 550, 551*f*
    electromyography, 551–552
    history, 548
    laboratory tests, 549–553
    neurologic examination, 548
    pelvic neurophysiology, 551–553
    penilo-cavernosus reflex, 552
    physical examination, 548
    pudendal nerve terminal motor latency, 552
    pudendal somatosensory evoked potentials, 552
    sphincter electromyography, 551–552
    ultrasound scan, 549
    uroflowmetry, 549, 550*f*
    videocystometry, 550–551
  in multiple sclerosis, 546
  neurogenic bladder. *See* Neurogenic bladder
  symptoms of
    in amyloid neuropathy, 547
    basal ganglia lesions and, 545
    brainstem lesions and, 545
    cerebral lesions and, 545–546
    in diabetic neuropathy, 546–547
    in immune-mediated neuropathies, 547
    in multiple system atrophy, 545
    in Parkinson disease, 545
    peripheral neuropathies and, 546–547
    in pure autonomic failure, 547
    spinal cord lesions and, 545–546
    types of, 544*t*, 545
    urinary tract infection screening, 549
L265P mutation
  in *MYD88* gene, 451
LSD. *See* Lysergic acid diethylamide (LSD)
L-type calcium channel receptors, 158
Lumbar disc disease, 375–376, 376*f*
Lumbar disc prolapse during pregnancy, 594–595
Lumbar puncture
  in bacterial meningitis, 685
  brain abscess and, 694
  in disordered consciousness, 1094
  epidermoid tumors after, 956
  headache and, 956
  hearing loss after, 956
  for viral meningitis, 747
Lumbar spine
  stenosis of, 376–377, 569–570
Lumbosacral plexopathy
  diabetic, 310
  metastatic, 494–495
  in neuroborreliosis, 712*t*
  obstetric-induced palsy of, 594–595
  in pregnancy, 595
  radiation-induced, 494, 534*t*, 535, 1062
  weakness and, 535
Lung transplantation, 796
Lungs, mechanical inputs from, 4–5
Lupus anticoagulant, 77, 175*t*, 176, 350, 469–470, 1030
Lupus anticoagulant (LA) assay, 176
Lupus headaches, 1052
Lyme disease, 352*t*, 353–354, 354*f*, 406, 710–714, 712*t*–714*t*, 845, 901, 1024, 1029*t*, 1037, 1059, 1091
  arthritis of, 708–709
  cerebrospinal fluid findings in, 713
  chronic, 711
  clinical features of, 709–712
  cranial nerves affected by, 711–712
  diagnosis of, 712–713
  ELISA results, 713
  endemic areas for, 714
  erythema migrans in, 352*t*, 353–354, 354*f*, 366*t*, 708*f*, 709–710
  general features of, 709–710
  geographic regions of, 708–709, 709*f*
  historical descriptions of, 707–708
  incidence of, 709*f*
  Ixodes ticks, 707–708, 708*f*
  laboratory tests, 712
  neuroborreliosis and, 352*t*, 354*f*, 710–712, 712*t*, 1044
  outcome of, 713–714
  prevalence of, 712–713
  rash in, 352*t*, 353–354, 354*f*, 366*t*, 708*f*, 709–710
  sensorineural hearing loss caused by, 406
  treatment of, 713–714, 714*t*
Lyme encephalopathy, 711
Lymphocytic chorio-meningitis virus (LCMV)
  encephalitis caused by, 756
  meningitis caused by, 742, 744*t*, 746–747
Lymphohistiocytosis
  hemophagocytic, 458–459
Lymphoma, 453
  Burkitt, 453–454, 493
  intracranial involvement in, 453
  intravascular, 454–455, 454*f*, 455*f*
  large B-cell, 453, 455, 495
  meningeal, 453
  neurocutaneous manifestations of, 352*t*
  neurologic complications of, 453
  primary CNS, 454, 776*t*, 778–779
  spinal cord involvement in, 453

Lymphomatoid granulomatosis, 455
Lymphoproliferative disorders, 464*t*, 514, 790–791, 796, 1059
Lysergic acid diethylamide (LSD), 643
  hyperthermia and, 666*t*

M

Ma2 antibodies, 508–509
Ma antibody, 510–511
Macroglobulinemia, 446, 449, 451–453, 506, 517, 1041, 1064*t*, 1071
Macrolides, 410, 619–620, 1075*t*
Macrophage activation syndrome (MAS), 459
Macrophagic myofasciitis, 622
Macro-reentrant arrhythmias, 81–82
Macular edema, 614
Maddox rod, 424
Magnesium
  disturbances of, 279–280, 1019–1020
  hypermagnesemia, 280
  hypomagnesemia, 280
Magnetic resonance angiography (MRA), 58, 94
  for carotid artery stenosis, 116
  for diagnostic evaluation of patients with stroke/TIA, 68
  for transient cerebral ischemic attacks, 584
Magnetic resonance imaging (MRI), 1059–1060
  acute disseminated encephalomyelitis, 762, 762*f*
  after cardiac arrest, 153
  alcoholic dementia, 629
  aneurysm clips and, 954
  arteriovenous malformation, 586*f*
  artifacts in, 954
  Behçet disease, 906
  brain abscess, 693–694
  cerebral toxoplasmosis, 826*f*, 827
  chorea, 1032
  communicating hydrocephalus, 1104*f*
  contraindications, 953–954
  contrast media for, 952–953
  Creutzfeldt–Jakob disease, 759–760, 760*f*
  delayed brain development, 54
  with diffusion-weighted imaging (DWI) sequences, 68
  disordered consciousness, 1093
  dural arteriovenous fistula in pregnancy, 588*f*
  dystonia, 1032
  embolic shower, 980
  encephalopathy-vasculopathy, 874–875, 874*f*
  epidural abscess, 697
  ferromagnetic artifacts in, 954
  hearing loss and, 954–955
  herpes simplex virus encephalitis, 750, 750*f*, 758–759
  HIV-associated dementia, 768, 769*f*
  hypertensive encephalopathy, 120*f*, 121
  intracerebral hemorrhage, 109–110
  intracranial atherosclerosis, 118
  intracranial hypotension, 917*f*
  intracranial neoplasms, 582
  ischemic stroke evaluations, 94
  lacunar infarct, 111–114, 112*f*
  manganese-induced parkinsonism, 656
  meningiomas, 872*f*
  metallic stents and, 954
  missile injury caused by, 954
  myelography versus, 955
  neurocysticercosis, 832, 833*f*
  neurologic complications of, 953–955
  neurosarcoidosis, 878, 878*f*
  nitrous oxide abuse, 644*f*
  pacemakers and, 953–954
  periventricular white matter disease, 114–115, 114*f*
  primary CNS lymphoma, 779
  progressive multifocal leukoencephalopathy, 757–758, 758*f*
  screening before, 954
  septic emboli, 89*f*
  septic encephalopathy, 995
  Sjögren syndrome, 891
  specific absorption rate, 954–955
  stroke detection by, 44
  subdural empyema, 697
  tissue heating caused by, 954–955
  for transient cerebral ischemic attacks, 584
  tuberculous meningitis, 721
Magnetic resonance spectroscopy (MRS), 54
Maintenance of wakefulness test, 916
Malabsorption syndromes, 208
  copper deficiency, 210, 236, 236*t*, 240–241, 443, 1072
  familial hypercholesterolemia, 208–209
  mechanisms of, 208
  pellagra, 209–210
  tropical sprue, 209
  vitamin E deficiency, 208
  Wernicke encephalopathy (WE), 209
Malaria
  antimalarial therapy for, 824
  cerebral, 821–825
  diagnosis of, 824
  global distribution of, 821–822, 823*f*
  laboratory tests for, 824
  manifestations of, 823
  parkinsonism and, 1044
  pathogenesis of, 823
  point-of-care diagnostics for, 824
  prevalence of, 821
  rapid diagnostic tests for, 824
  treatment of, 824
Malignant hyperthermia, 624, 662*t*, 664, 666*t*, 668, 967, 973, 980*t*, 985, 987–988, 1002, 1077*t*
Mammalian target of rapamycin (mTOR), 347, 797–798, 798*t*
Manganese, 196–197, 260, 632, 650, 655–656, 656*f*, 953, 1026, 1027*t*, 1036*t*, 1039*t*, 1042–1043
"Man-in-a-barrel" syndrome, 148
Marantic endocarditis. *See* Nonbacterial thrombotic endocarditis (NBTE)
Marble brain disease. *See* Carbonic anhydrase II deficiency
Marchiafava–Bignami disease, 357, 628*f*, 631–632
Marfan syndrome, 37–38, 186, 350
Marijuana, 644–645, 1020, 1036*t*, 1048*t*
Mastoiditis, 693–694, 695*t*, 696, 700
Maternal brachial plexopathy, 595
Maternal rubella, 590
Maternally inherited diabetes and deafness (MIDD), 408
Maximal inspiratory force (MIF), 7
McCune–Albright polyostotic fibrous dysplasia, 345
McLeod neuroacanthosis, 447
MDMA (ecstasy), 640
Measles, 406, 449, 763*t*, 847, 855, 858–859, 863, 865, 1029*t*, 1030
Measles, mumps, rubella vaccine, 854, 854*t*, 856*t*, 858–860, 864*t*
Mebendazole, for neurotrichinosis, 834
Mechanical thrombectomy, 58
Mechanical tremor, 1038
Mechanical valve, anticoagulant therapy in patients with, 96–97
Mechanical ventilation. *See also specific disorders*

  in end of life care, 1121
  failure to wean from, 998
  Guillain–Barré syndrome treated with, 13
  withdrawal of, 1116
Median neuropathy, 210. *See also* Carpal tunnel syndrome
Medically assisted suicide, 1112
Medication-overuse headache, 604, 970
Medication-related hemodynamic instability, 61
Medullary control of cardiovascular function, 158
Melanoma, 264, 324, 347, 528
  dermatomyositis and, 369, 897
  metastatic, 108, 320t, 347, 352t, 366t, 460, 476, 478f, 479, 481, 482t, 483, 488, 490–491, 493, 1018, 1061
  retinopathy associated with, 506t, 513
  vaccine and, 864
Melarsoprol, 829
MELAS. *See* Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS)
Melatonin, 914
  for delayed sleep phase disorder, 928–929
  for insomnia, 919–920
  for shift work disorder, 930
  for sleep-related eating disorders, 934t
Melatonin receptor agonists, 919–920
Memantine, 432, 480, 582, 769, 1100–1101
Membrane attack complex, 1080
Meniere disease, 400–401, 408
Meningeal leukemia, 352t, 447–448
Meningeal lymphoma, 453, 495
Meningiomas, 1059
  compressive optic neuropathy due to, 421f
  magnetic resonance imaging of, 872f
  in pregnancy, 323, 582
  in sarcoidosis, 872–873, 872f
  sex hormones and, 323
Meningitis
  aseptic. *See* Aseptic meningitis
  bacterial. *See* Bacterial meningitis
  blastomycotic, 812–813
  Candida, 810, 817–818
  carcinomatous, 1059
  chemical, 798t, 799, 813t, 840, 850
  coccidioidal, 352t, 808, 818
  cryptococcal, 776t, 779, 805–807, 809, 812–817, 842, 1018, 1029t, 1030
  differential diagnosis of, 812t
  eosinophilic, 458t, 822t, 834–835, 837
  fungal. *See* Fungal meningitis
  in infective endocarditis, 97
  meningococcal, 351–353, 354f, 684, 686, 689–690, 692
    vaccination for, 854–855, 856t
  myelography as cause of, 958
  neonatal, 695t
  neurocutaneous manifestations of, 351–353, 352t
  otogenic, 400
  tuberculous. *See* Tuberculous meningitis (TM)
  uveomeningitis, 355
  viral. *See* Viral meningitis
Meningitis, chronic, 839–851
  approach, 840–841
  definition, 840
  drug-induced meningitis, 850
  infectious causes, 841–847
    Aspergillus fumigatus, 843
    Candida species, 843–844
    Cryptococcus species, 841–843
    Mycobacterium tuberculosis, 844–845
    neuroborreliosis (Lyme) disease, 845
    neurocysticercosis, 846–847
    neurosyphilis, 845–846
    viral etiologies, 847
  inflammatory causes, 847–850
    IgG4-related disease, 849–850
    malignancy, 850
    neurosarcoidosis, 847–848
    primary central nervous system vasculitis, 848–849
    rheumatoid arthritis, 849
  recurrent meningitis, 850–851. *See also specific disorders*
Meningococcal meningitis, 351–353, 354f, 684, 686, 689–690, 689t, 692
  vaccination for, 854–855, 856t
Meningoencephalitis, 97
  embolization as cause of, 88–91
  granulomatous amebic, 829
  neurocutaneous manifestations of, 351–353
  primary amebic, 829, 830f
Meningomyelocele, 546, 570
Meningovascular syphilis, 180, 353t, 354, 583, 706–707, 711, 1091
Menkes disease, 210, 240
Menkes P-type ATPase (ATP7A), 240
Menopausal women, hormonal changes in, 562–563
Menopause, and stroke, 175
Menstrual cycle
  depression and, 326
  migraine and, 318
Meperidine, 318, 605–606, 641, 643, 664, 666t, 669–671, 686t, 987, 1036t, 1052
Mepolizumab, 458
Meralgia paresthetica, 202, 309, 595–596
Mercury, 103, 129, 652, 655, 1027t, 1036t, 1039t, 1042, 1063t, 1064t
Meropenem, 688t, 689t, 690, 694–695, 695t, 697, 699
Merozoites, 822–823
Mescaline, 643
Metabolic disorders. *See individual disorders*
Metabolic encephalopathy, 10, 793–794, 1088–1090, 1089t, 1094. *See also individual disorders*
Metaiodobenzylguanidine, 311
Metastases
  brain, 476–482
    chemotherapy for, 481
    clinical features of, 476–477
    diagnostic studies of, 477–478, 478f
    differential diagnosis of, 478
    epidemiology of, 476
    hematogenous dissemination of, 476
    neurologic manifestations of, 476–477
    pathology of, 476
    pathophysiology of, 476
    prognostic variables for, 478–479
    prophylactic cranial irradiation for, 481–482
    small cell lung cancer, 481–482
    solitary, 477f
    stereotactic radiosurgery, 480–481
    supportive treatment of, 479
    surgery for, 479–480, 480t
    targeted therapies for, 481
    treatment of, 479–482
    whole-brain radiotherapy for, 480, 480t
  intracranial dura, 483–484, 485f
  leptomeningeal, 490–493

- Metastases (*Continued*)
  - clinical features of, 491
  - definition of, 490
  - diagnostic studies of, 491–492, 491*f*
  - epidemiology of, 490
  - pathophysiology of, 490
  - prognosis for, 492–493
  - trastuzumab for, 530
  - treatment of, 492, 530
  - muscle, 496–497
  - pachymeningeal, 484
  - peripheral nervous system
    - peripheral nerves, 495–496
    - plexuses. *See* Metastatic plexopathy
  - skull-base
    - clinical features of, 482
    - cranial neuropathy and, 482, 483*t*
    - definition of, 482
    - diagnostic studies of, 482, 484*f*
    - differential diagnosis of, 483
    - epidemiology of, 482
    - magnetic resonance imaging of, 484*f*
    - pathophysiology of, 482
    - prognosis for, 483
    - treatment of, 483
  - spine/spinal cord
    - classification of, by anatomic location, 485, 486*t*
    - clinical features, epidural lesion, 486
    - clinical features, intramedullary lesion, 489
    - epidemiology of, 485
    - epidural spinal cord compression, 485–489
    - intramedullary, 489, 490*f*
    - pathophysiology, 486
    - treatment, 488–489
- Metastatic plexopathy
  - anatomic considerations, 493
  - brachial plexus, 493–494
  - cervical plexus, 493
  - clinical features of, 493
  - definition of, 493
  - diagnostic studies, 494
  - epidemiology of, 493
  - lumbosacral plexus, 494
  - pathophysiology of, 493
  - prognosis for, 495
  - radiation plexopathy versus, 494–495
  - treatment of, 495
- Methamphetamines, 605, 638–639, 639*f*
- Methanol poisoning, 416*t*, 1025–1026, 1027*t*, 1036*t*, 1039*t*, 1042–1043
- Methionine synthase, 239, 442, 644
- Methotrexate, 239, 239*t*, 266, 394, 482*t*, 492, 496, 522*t*, 523–524, 523*t*, 530, 604, 605*t*, 621, 738, 779, 798*t*, 847, 849, 882–883, 889, 892, 897, 899–900, 902, 904, 1018, 1080
  - intrathecal, 530, 530*t*
  - neurologic complications of, 522*t*, 523–524
  - stroke-like syndrome caused by, 523–524
  - for systemic lupus erythematosus, 889
  - toxicity caused by, 530*t*
- Methyl *n*-butyl ketone, 129, 652
- Methylcobalamin, 236–237
- Methyldopa, 133, 585, 608, 611, 616, 666*t*
- Methylene tetrahydrofolate reductase gene (*MTHFR*), 173, 239, 471, 473
- 3,4-Methylenedixymethamphetamine (MDMA, ecstasy), 640
- Methylmalonic acid (MMA), 236*t*, 238, 442, 1072
- Methylmalonic aciduria, 357*t*
- Methylmercury, 857
- Methylphenidate, 605, 605*t*, 608, 611, 614, 770, 922*t*, 1026, 1027*t*
- Methylphenyl tetrahydropyridine (MPTP), 643, 659, 1042
- Methylprednisolone. *See* Corticosteroids
- 5-Methylenetetrahydrofolate reductase, 173, 239, 320, 471
- Metoclopramide, 311, 331*t*, 592, 610, 612, 612*t*, 932*t*, 966, 987, 1026, 1027*t*, 1036*t*, 1039*t*, 1042, 1049
- Metoprolol, 614, 616, 1051
- Metronidazole, 198, 205, 306*t*, 605*t*, 614–615, 617–618, 617*t*, 689*t*, 694, 697, 699, 831, 1063*t*, 1064*t*
  - for brain abscess, 694–695, 695*t*
- mGluR1 antibodies, 510–511
- *MGMT* gene, 532
- MGUS. *See* Monoclonal gammopathy of undetermined significance (MGUS)
- Miconazole, for coccidioidal meningitis, 818
- Microadenomas, pituitary, 328–329, 329*f*, 331–332
- Microscopic polyangiitis (MPA), 900, 1066
- Microsomal triglyceride transfer protein gene, 208–209, 446–447
- Microtubule agents
  - ixabepilone, 522*t*, 525–526, 617, 617*t*
  - neurologic complications of, 525–526
  - taxanes, 411, 522*t*, 525, 617, 617*t*
- Microvasculitis, peripheral neuropathy caused by, 517
- Micturition syncope, 133
- Midazolam, 151, 986*t*, 988–989, 1036*t*, 1116
- Middle cerebral artery (MCA), 55*f*, 69, 88–91, 115, 117, 148, 176*f*, 270, 319, 639*f*, 693, 753, 1097*f*
- Middle ear infections, 693, 696. *See also* Otitis media
- Middle fossa syndrome, 482, 483*t*
- Midodrine, 132, 141*t*, 142*t*, 143–144, 257, 311
- Migraine, 183, 318–319, 575, 581–582, 1054. *See also* Headache
  - with aura, 1047–1050
  - catamenial, 318
  - cardiovascular disease and, 1049
  - cerebrovascular disease and, 1050
  - comorbidity of, 1047–1048, 1053*t*
  - dizziness associated with, 402–404
  - epilepsy and, 1047–1048
  - estrogen-related, 319
  - gender predilection, 318
  - gut dysmotility and, 226
  - hypertension and, 1049–1050
  - ischemic heart disease and, 1047–1048
  - menstrual, 318
  - multiple sclerosis and, 1048
  - oral contraceptives and, 318–319
  - patent foramen ovale (PFO) and, 1048–1049
  - perimenopausal, 318
  - perioperative considerations, 969–970
  - in pregnancy, 581–582
    - acute treatment, 581
    - lactation, treatment during, 582
    - preventive treatment, 581–582
  - Raynaud phenomenon and, 1052
  - sex hormones and, 318–319
  - sleep deprivation and, 937
  - stroke prevention in, 183
  - in systemic lupus erythematosus, 888
  - thyroid disease and, 1051
  - triggers for, 937
- Migraine medications and stroke, 185
- Migrainous stroke, 183

Miller Fisher syndrome, 426, 429, 453, 618, 1069–1070. *See also* Guillain–Barré syndrome
Minamata disease, 1026
Minimally conscious state, 1097–1098, 1117–1119
Mirabegron, 554
Misalignment, ocular, 424–425
Misonidazole, 605*t*, 614, 617–618
Mitochondrial cytopathies, 218, 223*t*, 1084
Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), 408, 619
Mitochondrial myopathies, 16, 231, 280, 619, 622–623, 1076, 1083
Mitochondrial transcription factor A, 291
Mitral valve prolapse, 66, 69, 75, 124, 131
Mitral valve regurgitation, 75
Mitral valve stenosis and rheumatic heart disease, 76
Mixed apnea, 16, 925
Modafinil, 922–923, 922*t*, 927, 929–930
Mollaret meningitis, 745*t*, 746
Mollaret triangle, 432
Monoamine oxidase inhibitors, 119, 605, 608–609, 612–616, 664, 666*t*, 923, 935, 1036*t*, 1048*t*
  for cataplexy, 923
  hyperthermia and, 666*t*
Monoclonal antibodies, 799. *See also individual agents*
Monoclonal gammopathy of undetermined significance (MGUS), 449, 451–453, 1070
Monocular diplopia, 424
Monocular "shimmering" nystagmus, 433
Mononeuritis multiplex, 98, 205, 205*t*, 354, 357, 365, 368, 393, 446, 455, 515, 517, 618, 732, 734, 856*t*, 875, 889, 896–897, 902, 1067–1068
Mononeuropathies. *See also individual nerves and disorders*
  aortic disease as cause of, 31–32
    femoral nerve, 31–32
    left recurrent laryngeal nerve, 31
    obturator nerve, 32
  hyperthyroidism and, 295
  in infective endocarditis, 98
  traumatic, in pregnancy, 596
Mononeuropathy multiplex, 211, 458, 712, 712*t*, 895–896, 900, 902, 1065
Monophosphoryl lipid A (MPL), 857
Mood disorders, drug-induced, 608. *See also individual disorders*
Morphine, 315, 318, 605*t*, 614, 616, 752, 986, 986*t*, 1014*t*, 1036*t*, 1052, 1115–1116, 1120–1121
Morvan syndrome, 502, 503*t*, 507, 519
Motor disorders, functional, 942–943
Motor evoked potentials (MEPs), 40, 564, 945
Motor neuron disease, 514, 533–534
  amyotrophic lateral sclerosis. *See* Amyotrophic lateral sclerosis (ALS)
  anterior horn cell diseases, 1058–1059
  progressive muscular atrophy variant of, 292
  spinal cord ischemia and, 27, 27*f*
Motor neuropathy, 12*t*, 14, 205, 357*t*, 515, 525, 597, 617–618, 1001, 1063, 1066*t*, 1067–1068, 1073
Movement disorders, 11–12, 258, 1023–1046
  autoimmune disorders and, 1030–1031
  chorea. *See* Chorea
  drug-induced, 609, 1026–1028, 1034–1039, 1042
  dystonia. *See* Dystonia
  emergencies
    in perioperative period, 966–967
  fungal infections and, 1030
  hyperkinetic disorders, 12. *See also individual disorders*
  hyperthyroidism and, 296–298
  hypokinetic disorders, 11. *See also individual disorders*
  hypoxia-ischemia, 1024–1025, 1033–1034, 1038, 1041–1042
  infections that cause, 1028–1030, 1029*t*, 1037, 1040, 1043–1044
  inflammatory disorders and, 1030–1031, 1034, 1041, 1044–1045
  metabolic disorders and, 1031–1032, 1034, 1040, 1043
  myoclonus. *See* Myoclonus
  paraneoplastic disorders and, 1031, 1037, 1044–1045
  parasitic infections and, 1030
  parkinsonism. *See* Parkinsonism
  postoperative care of, 966
  in pregnancy, 591–592
    chorea, 591
    dystonia, 592
    essential tremor, 592
    Parkinson disease, 592
    restless legs syndrome, 591–592
    Tourette syndrome, 592
    Wilson disease, 592
  preoperative care of, 966
  sex hormones and, 321–322
  stroke as cause of, 1024
  toxin-related, 1025–1026, 1035, 1039–1040, 1042–1043
  treatment of, 1032–1033, 1038, 1041, 1045–1046
Movement disorders, acute-onset, 60
Moxifloxacin, 724, 736
Moyamoya syndrome, 58, 179, 299, 444–445, 535, 535*t*
MPR1 gene, 806–807
Mucopolysaccharidoses, 408
Mucormycosis, 179*t*, 264, 792, 803–805, 810–811, 818–819
Multidrug therapy (MDT), for leprosy, 365, 728, 734, 738–740
Multifocal motor neuropathy, 12*t*, 14, 205, 597, 618, 1063, 1066*t*, 1067
Multimodal prognostication algorithms, after cardiac arrest, 154
Multiple myeloma, 182, 279, 442, 446, 449–450, 452, 467, 486, 486*t*, 517, 528, 617, 1059, 1064*t*, 1065, 1071
Multiple sclerosis
  abnormal thermal regulation and, 662, 663*t*
  alemtuzumab and, 458, 462–463
  anesthesia considerations in, 967
  ankylosing spondylitis and, 391
  bladder dysfunction in, 546, 553*f*, 554–556
  cardiac irregularities and, 165
  constipation and, 223, 228
  detrusor overactivity in, 546
  disease-modifying therapies (DMT) for, 800–801
  erectile dysfunction in, 568
  exacerbations of, 967
  general anesthesia and, 967
  incontinence and, 223–224, 228
  intrathecal baclofen for spasticity in, 967
  lower urinary tract dysfunction in, 546, 553–554
  and migraine, 1048
  ocular findings in, 432–433
  optic neuritis and, 416
  perioperative considerations, 967
  postoperative considerations, 967
  postural hypotension in, 127
  predisposing factors, 324
  pregnancy and, 324, 592–594
  preoperative considerations in, 967
  seizures in, 1016
  sex hormones and, 324
  sexual dysfunction in, 565, 568, 573, 575

Multiple sclerosis (*Continued*)
  sleep hypoventilation syndrome, 17*t*
  spinal cord injury and, 227–228
  thyroid disease and, 301
  ulcerative colitis and, 206
  vaccination and, 862–863, 864*t*
  vitamin D and, 247, 380
Multiple sleep latency test
  for idiopathic hypersomnias, 923
  indications for, 916
  for narcolepsy, 922
Multiple system atrophy (MSA), 11, 129, 194
  cerebellar, 1101
  dementia and, 1100*t*, 1101, 1105
  dysautonomia in, 127, 129–130, 136*f*, 139*f*, 143–144, 227–228, 988, 1105*t*
  erectile dysfunction and, 567
  gut dysmotility and, 224, 227
  neurogenic bladder in, 545, 548*t*, 552, 1109–1110
  parkinsonian, 194, 1101
  perioperative care, 998
  respiratory dysfunction in, 9, 11, 17*t*, 132
  sexual dysfunction in, 567, 573
  sleep apneas in, 11, 1109
  sleep disorders in, 1109
  sphincter electromyography in, 552
  subtypes of, 1101
  thermoregulation and, 663*t*
Mumps virus, 743*t*, 747, 859–860
Murine typhus, 352*t*
Muscle
  disorders of. *See* Myopathy
  metastases to, 496–497
Muscle biopsies, 997
Muscle diseases that cause gut dysmotility, 231–232
Muscle-specific kinase (MuSK), 430, 504*t*, 518–519, 620, 1076
Muscle-specific receptor tyrosine kinase, 1076
Muscular dystrophies, 15, 74, 231, 327, 378*t*, 457, 571, 624, 997*t*, 1076
  malignant hyperthermia and, 624, 664, 972–973, 988
  perioperative considerations in, 971–973
  respiratory dysfunction associated with, 15
Mushroom intoxication, 643
Myasthenia gravis (MG), 207, 260, 425–426, 460, 518–519, 997, 1076
  checkpoint inhibitors and, 460, 529
  congenital, 598
  diagnosis of, 1076
  extraocular movement limitations in, 426*t*
  extraocular muscle weakness and, 430
  generalized, 1076
  hyperthyroidism and, 292, 295, 1076
  hypothyroidism and, 291
  inflammatory bowel disease and, 205*t*, 207
  magnesium sulfate and, 597–598
  neonatal, 598
  ocular, 425, 425*t*, 426*t*, 429–430, 1076
  paraneoplastic, 500–502, 504*t*, 506*t*, 517
  postoperative, 973
  in pregnancy, 597–598
  perioperative care of, 973, 988
  prevalence of, 429
  regional anesthesia for, 973
  respiratory failure and, 12*t*, 14–15
  sleep apneas and, 17*t*
  thymoma and, 430, 500–501, 518–519, 973, 1076
  vaccination and, 856*t*
Mycobacterium leprae, 365, 727–731, 735–737, 739–740
Mycobacterium tuberculosis, 717–718, 780, 844, 1059, 1103
  diagnostic testing, 844
  presentation, 844
  risk factors, 844
  treatment, 844–845
Mycophenolate mofetil, 430, 512, 514, 522*t*, 597, 621, 798*t*, 799–800, 826, 848, 882–883, 889, 892, 899, 902, 1067, 1070, 1080–1081
Mycoplasma pneumoniae, 748, 1028–1030, 1044, 1069
Mycotic aneurysms, 59–60, 77, 87–91, 350, 587, 645, 790, 792, 804, 844
  angiography of, 94–95, 97
  aortitis, 36*t*
  causes of, 88–91
  in infective endocarditis, 93, 97, 645
  and intracranial hemorrhage, 94, 350, 587, 645
  natural history of, 97
  rupture of, 97, 645
  screening for, 94
  treatment of, 97, 645
MYD88 gene, 454
  L265P mutation in, 451
Myelin oligodendrocyte glycoprotein (MOG), 418, 502, 762, 1016
Myelin-associated glycoprotein, 451
Myelitis, paraneoplastic non-necrotizing, 514
Myelofibrosis, 457
Myelography, 955–958
  complications of, 956–958
  complications of C1–C2 puncture, 957
  computed tomography, 955
  indications for, 955
Myelomatosis, 449–451
  cranial myeloma, 449–450
  immunodeficiency in, 451
  metabolic complications of, 451
  neurologic complications of, 449–451
  peripheral neuropathy and, 450–451
  platelet function abnormalities in, 463
  spinal myeloma, 449
Myelopathy
  ankylosing spondylitis and, 390
  antiphospholipid syndrome, 470
  Behcet disease and, 355–356
  chemotherapeutic agents and, 523*t*, 527, 530, 616
  copper deficiency, 210
  corticosteroids and, 799
  Cushing disease, 332
  cycticercosis and, 832
  degenerative spine disease and, 373–376
  hepatic, 193–196, 198–199
  in HTLV-I infection, 589, 782
  in hyperparathyroidism, 337
  in hypoparathyroidism, 278
  inflammatory bowel disease and, 202–203, 206
  ischemia and, 27, 453–454, 465, 616
  ischemic, 26–27, 453, 465
  ln Sjögren syndrome, 891
  Lyme borreliosis and, 354, 356, 711
  lymphoma and, 454–455, 514
  metastatic, 489, 514, 1059
  myeloma, 449
  non-Wilsonian hepatocerebral degeneration, 632
  osteomalacia and, 381
  osteoporosis and, 379

  in Paget disease, 385
  paraneoplastic, 448, 453, 501*t*, 502*t*, 508, 513
  from radiation, 531*t*, 533–534
  in rheumatoid arthritis, 364–365, 895
  in sarcoidosis, 871*t*, 875
  in schistosomiasis, 836
  in sickle cell disease, 444
  in Sjögren syndrome, 365
  in tuberculosis, 388–389, 723
  vacuolar, in HIV-infected patients, 781, 783
  vitamin B_{12} deficiency and, 210, 236–237, 443, 590
Myenteric plexus, 218, 219*f*, 221, 228, 230, 1109
Myocardial infarction
  acute, 74, 80
  stroke and, 159–160
Myocardial ischemia, 70
Myocardial necrosis, 160
Myocardial revascularization surgery, 51
Myocardial stress, 70
Myocardium, 157, 161*f*, 162
Myoclonic encephalopathy, 606
Myoclonus, 1033–1038
  action, 1037
  acute posthypoxic, 1033
  antiphospholipid antibody syndrome and, 1034
  autoimmune disorders and, 1034
  bacterial infections and, 1037
  celiac disease and, 1034
  chronic posthypoxic, 1033–1034
  cortical, 1038
  diagnosis of, 1037–1038
  distribution of, 1033
  drug-induced, 611, 1034–1037, 1036*t*
  HIV infection and, 1037
  hyperglycemia and, 1034
  hypoxia-ischemia and, 1033–1034
  infections and, 1037
  inflammatory disorders and, 1034
  metabolic disorders and, 1034
  multifocal, 1033, 1037
  in neuroleptic malignant syndrome, 1034–1035
  paraneoplastic disorders and, 1037
  pellagra and, 1034
  physical agents that cause, 1037
  posthypoxic action, 1033
  in renal failure, 1008
  in serotonin syndrome, 1035
  spinal, 1037
  status epilepticus, 149–151, 1014–1015, 1033
  tardive, 1035
  toxin-induced, 1034–1037, 1036*t*
  treatment of, 1033, 1038
  uremic encephalopathy and, 252, 1034
  vitamin B_{12} deficiency and, 1034
Myofibrillar necrosis, 160
Myofibrillar proteins, 1004
Myoglobinuria, 12, 278, 613, 621–622, 624, 634, 998*t*, 1003, 1005, 1078–1079, 1082–1084, 1083*t*
Myokymia, 433, 509, 519, 534–535, 624, 1061
Myopathy, 15–16, 369. *See also* Cardiomyopathies
  acanthocytosis and, 447
  acromegaly and, 1077
  acute necrotizing, 634
  alcohol-related, 634–635, 1082
  cachectic, 1005
  causes of, 1077*t*
  celiac disease and, 204
  central core, 664, 973
  chemotherapy and, 526*t*, 528
  chronic, 634–635
  congenital myopathies, 15, 664
  in connective tissue disorders, 897–898
  corticosteroid, 16, 623, 799, 900, 1077
  critical illness. *See* Critical illness myopathy
  Cushing disease and, 332, 334*t*
  dermatomyositis, 369
  disuse, 998*t*
  drug-induced, 620–625, 1083
    acute quadriplegic myopathy, 623–624
    acute rhabdomyolysis, 622
    autophagic myopathies, 624
    cholesterol-lowering agents, 620–621, 622*f*
    cramps, 624
    glucocorticoid myopathy, 623
    inflammatory myopathies, 621–622
    malignant hyperthermia, 624
    mitochondrial myopathies, 622–623
    myalgia, 624
    potassium-related myopathies, 623
    twitches, 624
  endocrine-related, 1077–1078
  evaluation of, 1076
  hepatitis C virus infection and, 211
  HIV infection and, 782, 1078
  hyperparathyroidism and, 279, 1077–1078
  hyperthyroidism and, 292–293, 1077–1078
  hypoparathyroidism and, 338
  hypothyroidism and, 386–387, 1077–1078
  inclusion-body, 386–387, 501*t*, 520, 782, 897, 1077*t*, 1080–1081
  infectious, 1078–1079
  inflammatory
    clinical presentation of, 1079–1081
    dermatomyositis, 369, 369*f*, 500–501, 506*t*, 519, 621–622, 897, 1079–1080
    inclusion-body myositis, 501*t*, 520, 782, 897, 1077*t*, 1080–1081
    polymyositis. *See* Polymyositis
    sarcoidosis, 1081. *See also* Sarcoidosis
  inflammatory bowel disease and, 205*t*, 206
  inflammatory myopathies, 15
  malignant hyperthermia in, 973
  metabolic, 1082
  mitochondrial, 221, 231, 279–280
  muscular dystrophies, 15
  necrotizing, 621, 622*f*, 1079, 1081
  nemaline rod, 664
  osteomalacia and, 202, 380, 1077–1078
  paraneoplastic, 501*t*, 506*t*, 508, 519–520
  perioperative considerations, 972–973
  polyneuropathy and, 998*t*
  potassium and, 1082
  respiratory dysfunction associated with, 15–16
  sarcoidosis and, 353*t*, 876–877, 882, 884, 1081
  statin-induced, 621, 622*f*, 1083
  thalassemia and, 445
  thyrotoxic, 292–293
  toxic, 1082
  uremic, 258, 1082
  vitamin D deficiency, 247, 380–381
  vitamin E deficiency, 242
  Whipple disease and, 207
Myositis, 897
  inclusion-body, 501*t*, 520, 782, 897, 1077*t*, 1080–1081

Myositis (*Continued*)
  toxoplasmosis and, 1079
  viral, 1078–1079
Myotonia
  drug-induced, 624
  hypothermia and, 669
Myotonic dystrophy
  anesthetics and, 624, 973
  bladder involvement and, 547
  congenital, 599
  megacolon and, 231, 547
  in pregnancy, 598–599
  respiratory dysfunction in, 15
  sexual dysfunction and, 327, 571
Myxedema coma
  clinical features of, 287
  in elderly, 287
  hypothermia and, 670
  treatment of, 287
Myxoma, atrial, 66, 73, 182

N

N20 response, 150–152, 154, 1094
Nab-paclitaxel, 522*t*, 523*t*, 525
Nadolol, 1041, 1049
Naegleria fowleri, 822*t*, 829
Nail fold fibroma, 346*f*
Naloxone, 642, 980, 987
Naratriptan, 1050
Narcolepsy, 920–923
  age of onset, 920
  body mass index and, 921
  with cataplexy, 915, 921
  clinical features of, 921
  definition of, 920
  diagnosis of, 921–922
  disturbed nocturnal sleep and, 921
  excessive daytime sleepiness in, 921–923
  hypnagogic hallucinations and, 921
  hypocretin-1 levels in, 922
  multiple sleep latency test of, 922
  nonpharmacologic treatments of, 923
  pharmacologic treatments of, 922–923, 922*t*
  polysomnography of, 921–922
  REM sleep behavior disorder and, 921
  sleep attacks and, 921
  sleep paralysis and, 921
  symptoms of, 921
Narcotics, 221, 267, 378, 608, 970, 1036*t*
Natalizumab, 593, 606, 742, 745*t*, 757–758, 800, 800*t*
  during pregnancy, 593
National Vaccine Injury Compensation Program, 855–856, 859
Native valve endocarditis
  anticoagulation in, 96
  hemorrhagic complications of, 96
N-butyl-deoxynojirimycin, 467–468
Near-infrared spectroscopy monitoring, 49
Necrotizing autoimmune myopathy (NAM), 621
Necrotizing myelopathy, acute, 448, 453, 506*t*
Necrotizing myopathy, 15, 501*t*, 506*t*, 520, 621, 622*f*, 624, 634–635, 997*t*, 998*t*, 1002, 1005, 1058, 1081, 1083
Needle electromyography, 13–14, 33, 238, 257, 306, 551, 652, 733, 1003*t*
Neisseria meningitidis, 683, 689–690, 787–788
Nelarabine, 522*t*, 523*t*, 525
Nemaline rod myopathy, 664, 782, 1078
Nematodes
  Angiostrongylus cantonensis infection, 834–835
  Gnathostoma spp., 835
  gnathostomiasis, 835
  loiasis, 836
  onchocerciasis, 836
  strongyloidiasis, 834, 834*f*
  trichinosis, 834
  types of, 1079
  visceral larval migrans, 835–836
Neonates. *See also* Infant(s)
  AIDS in, 590
  balloon atrial septostomy in neonates with TGA, 56
  brain abscess in, 693
  brain injury in neonates with CHD, 55–56
  cardiac surgery, adolescent survivors of, 61–62
  congenital heart disease. *See* Congenital heart disease, children with
  maternal infections and the neonate, 588–590
  meningitis in, 695*t*
  myasthenia gravis in, 598
  phenylketonuria in, 590–591
  "silent" brain injury in, 55–56
  tetanus in, 589
Neoplastic aneurysms, 182
Nephrogenic diabetes insipidus, 334, 336
Nephrogenic systemic fibrosis, 952
Nephrotic syndrome, 177, 259–260, 500*t*
Nerve conduction studies, 238
  in critical illness myopathy, 1003
  in neurosarcoidosis, 878
  occupational neurotoxin exposure, 650
Nerve growth factor (NGF), 308, 729, 1068
Nerve root stimulators, 555
Neurally mediated syncope, 133
Neuraxial anesthesia, 967
Neuroacanthocytosis. *See* Acanthocytes/acanthocytosis
Neuro-Behçet disease. *See* Behçet syndrome
Neuroblastoma
  neurocutaneous manifestations of, 362*t*
  opsoclonus-myoclonus and, 512
Neuroborreliosis (Lyme) disease, 352*t*, 353–354, 354*f*, 406, 710–714, 712*t*–714*t*, 845, 1024, 1029*t*, 1037, 1059, 1091. *See also* Lyme disease
  diagnostic testing, 712–713, 845
  presentation, 710–712, 845
  risk factors, 708–709, 845
  treatment, 713–714, 845
Neurocardiogenic injury, mechanism of, 160
  catecholamine surge on cardiomyocytes, 160
  catecholamine surge on coronary microvasculature, 161–162
Neurocutaneous disorders/syndromes
  antiphospholipid syndrome, 348*t*, 350–351
  ataxia in, 362–364
  Behçet disease, 352*t*, 355–356
  dermatomyositis, 369, 369*f*, 500–501, 506*t*
  endocarditis, 348*t*, 350
  Fabry disease, 347–349, 348*t*
  Hartnup disease, 362*t*, 364
  hereditary hemorrhagic telangiectasia, 348*t*, 349–350
  homocystinuria, 348*t*, 350
  leprosy. *See* Leprosy
  Lyme borreliosis, 352*t*, 353–354, 354*f*, 406, 710–714, 712*t*–714*t*, 845, 901, 1024, 1028*t*, 1037, 1059, 1061. *See also* Lyme disease

  - melanoma, 347
  - meningococcal meningitis, 351–353, 353*f*
  - neurofibromatosis, 344–345, 344*f*, 408
  - otoneurologic manifestations of, 408
  - peripheral neuropathy, 365–369, 366*t*
  - Refsum disease, 362*t*, 363–364, 367*t*, 1065*t*, 1074
  - rheumatoid arthritis, 364–365
  - sarcoidosis, 353*t*, 355
  - seizures and, 359–362, 832
  - Sjögren syndrome, 353*t*, 365
  - stroke, 347–351
  - Sturge-Weber syndrome, 359–360, 360*f*
  - syphilis, 353*t*, 354–355, 354*f*, 355*f*
  - systemic sclerosis, 368
  - systemic vasculitis, 368–369, 368*f*
  - Takayasu arteritis, 348*t*, 351
  - tuberous sclerosis, 345–347, 346*f*
  - tumors, 344–345
- Neurocutaneous melanosis, 347, 347*f*, 348*t*, 366*t*
- Neurocysticercosis, 822*t*, 832–833, 833*f*, 840*t*, 846–848, 1029*t*, 1037, 1044
  - diagnostic testing, 832, 846–847
  - presentation, 832, 846
  - risk factors, 832, 846
  - treatment, 833, 847
- Neurodegeneration with brain iron accumulation type 1, 446
- Neurodegenerative disease, after head injury, 679
- Neuroendocrine tumors, 340, 1060
- Neurofibromas, dermal, 345
- Neurofibromatosis, 58, 74, 230, 340, 344, 1063–1064
  - description of, 1063–1064
  - gut dysmotility and, 230
  - otoneurologic manifestations of, 404*f*, 408
  - type I, 58, 230, 340, 344–345, 346*f*, 495
  - type II, 345, 404*f*, 408
- Neurofilament light chain (NFL), 154
- Neurogenic bladder, 541, 544–548. *See also* Lower urinary tract dysfunction
  - autonomic neuropathy and, 517, 547
  - autonomous, 546
  - basal ganglia lesions and, 545
  - brainstem lesions, 545
  - cerebral lesions and, 544–545
  - complications of, 553
  - cystometry evaluations, 550
  - diabetic neuropathy, 546–547
  - diagnostic evaluation of, 544*t*
  - dysfunction and, 544–548
  - Fowler syndrome, 547–548
  - investigations of, 549–553
  - management of, 553–556
  - multiple system atrophy and, 546, 1109–1110
  - overactive, 545–546
  - peripheral neuropathies and, 547
  - spinal cord lesions, 545–546
  - storage dysfunction
    - antimuscarinic medications for, 554
    - botulinum toxin for, 554–555
    - cannabinoids, 554
    - desmopressin for, 554
    - general measures for, 554
    - nerve root stimulators for, 555
    - nerve stimulation for, 555
    - percutaneous tibial nerve stimulation for, 555
    - permanent indwelling catheter, 556
    - sacral neuromodulation for, 555
    - surgery for, 555–556
    - vanilloids for, 555
  - voiding dysfunction, 553–554
- Neurogenic claudication, 28
  - coarctation of the aorta and, 39
  - description of, 376–377
  - intermittent, 28
- Neurogenic pulmonary edema, 9–10, 12
- Neurogenic thoracic outlet syndrome, 1062, 1062*f*
- Neuroleptic antiemetics, 1053*t*
- Neuroleptic malignant syndrome, 11, 612–613, 1034–1035
  - antidopaminergic medications and, 985
  - characteristics of, 612–613
  - clinical features of, 985
  - disseminated intravascular coagulation and, 464*t*
  - dopamine-depleting agents and, 1035
  - drugs that cause, 612–613, 966
  - postoperative, 985
  - serotonin syndrome versus, 613, 985, 1034–1035
  - sex steroids and, 323
  - thermoregulatory system overload and, 662*t*, 664, 666*t*
  - treatment of, 668, 966, 1034–1035
- Neuroleptics, 610, 920, 969, 1021, 1026, 1049, 1051–1052, 1053*t*, 1083*t*, 1101, 1107, 1115
- Neurologic complications
  - of therapies for hematologic malignancies, 459–460
    - checkpoint inhibitors, 459–460
    - chimeric antigen receptor (CAR) T-cell therapies, 459
- Neurologic injury
  - cardiac biomarkers of, 162
    - B-type natriuretic peptide (BNP), 163
    - creatine kinase (CK)-MB, 162
    - troponin, 162–163
  - prevention of, 45
- Neurolymphomatosis, 495–496, 782, 1066*t*, 1067
- Neuromuscular blocking agents
  - description of, 971
  - hypothermia and, 667*t*
  - mechanical ventilation withdrawal and, 1116
  - polyneuropathy and, 1002
- Neuromuscular junction/transmission disorders, 14–15, 429–430, 620–625, 1074–1076
  - drugs that cause, 620–625
  - Lambert–Eaton myasthenic syndrome. *See* Lambert–Eaton myasthenic syndrome (LEMS)
  - list of, 1075*t*
  - myasthenia gravis. *See* Myasthenia gravis (MG)
  - neurophysiologic studies of, 429–430
  - paraneoplastic, 518–519
- Neuromyelitis optica, 204, 228, 416–419, 416*t*, 501*t*, 502*t*, 662, 762, 848
- Neuromyelitis optica (NMO) spectrum disorder, 10, 514, 888–889
- Neuromyotonia, 506*t*, 519
- Neuron-specific enolase (NSE), 49, 149–150, 153, 674–675, 995
- Neuro-ophthalmologic disorders
  - abducens nerve palsy, 429
  - afferent visual disturbance, 415–424
    - description of, 415–424
    - idiopathic intracranial hypertension, 422–423, 422*f*, 423*f*, 457, 583, 604, 711
    - optic neuropathy. *See* Optic neuropathy
    - papilledema, 422, 422*f*, 422*t*
    - retrochiasmal vision loss, 423–424
  - efferent visual disturbance, 424–433
    - alternate cover test for, 424

- Neuro-ophthalmologic disorders (*Continued*)
    - clinical assessment of, 424–426
    - diplopia, 424, 430–431
    - internuclear ophthalmoplegia, 429
    - Maddox rod, 424
    - mechanical causes of diplopia, 430–431
    - Miller Fisher syndrome, 429
    - motility examination, 425
    - neuromuscular junction dysfunction, 426*t*, 429–430
    - nystagmus, 431–433
    - ocular dysmotility, 427
    - ocular misalignment, 424
    - saccadic intrusions, 433
  - idiopathic intracranial hypertension, 422–423, 583, 604, 711. *See also* Intracranial hypertension
  - ischemic disorders that cause, 420*t*
  - manifestations of, 416*t*
  - oculomotor nerve palsy, 427–428
  - pupil
    - Adie tonic, 436
    - afferent defect of, 434
    - anatomy of, 433–434
    - anisocoria, 132, 428, 434–436
    - Argyll Robertson, 434, 706–707
    - light response, 434
    - near response, 434
    - swinging flashlight test of, 434
    - tonic, 436
  - trochlear nerve palsy, 428–429
- Neuropathic pain, 892
  - diabetes mellitus and, 305, 308, 314–315
  - Fabry disease and, 267–269
  - HIV associated neuropathy and, 781
  - intermittent porphyria, acute, and, 1017
  - leprosy and, 729, 732
  - neuromyotonia and, 519
  - pathophysiology of, 314
  - restless legs syndrome and, 932
  - treatment of, 267, 315, 634, 781, 783, 892, 932, 1068
  - and vitamin B_{12}, 443
- Neuropathy. *See also individual disorders*
  - alcoholic, 1072
  - alcohol-related, 634–635
  - autonomic. *See* Autonomic neuropathy
  - bladder, 312
  - critical illness polyneuropathy. *See* Critical illness polyneuropathy (CIP)
  - drug-induced, 450, 616–619, 1073
  - entrapment. *See* Entrapment neuropathy
  - fibular, 495, 596, 730, 895–896, 983–984, 1063–1064
  - gastrointestinal, 311
  - Guillain–Barré syndrome. *See* Guillain–Barré syndrome
  - hereditary
    - adrenomyeloneuropathy, 1073
    - clinical presentation of, 1073
    - Fabry disease, 1063*t*, 1073
    - porphyria, 1073–1074
    - Refsum disease, 362*t*, 363–364, 366*t*, 1065*t*, 1074
    - Tangier disease, 1063*t*, 1074
  - HIV, 781–782, 1064*t*, 1065*t*, 1068. *See also* Human immunodeficiency virus
  - infectious, 1068
  - lead, 653–654
  - in leprosy, 365–367
  - multifocal
    - causes of, 1066*t*
    - definition of, 1065–1068
    - hepatitis B, 1066–1067
    - hepatitis C, 1067
    - idiopathic immune-mediated, 1067
    - motor, 12*t*, 14, 205, 597, 618, 1063, 1066*t*, 1067
    - vasculitic neuropathy, 1065–1066
  - in myelomatosis, 450–451
  - neoplastic, 1071
  - neuraxial blockade and, 983
  - nutritional
    - copper deficiency, 210, 240, 1072
    - vitamin B_1 deficiency, 242–243, 1071–1072. *See also* Korsakoff syndrome; Thiamine deficiency; Wernicke encephalopathy
    - vitamin B_6 deficiency, 236*t*, 245–246, 306*t*, 1060*t*, 1072
    - vitamin B_{12} deficiency. *See* Vitamin B_{12} deficiency
    - vitamin E deficiency, 208, 242, 1072
  - paraneoplastic, 229, 450, 500–501, 502*t*, 515, 517, 1071
  - peripheral. *See* Peripheral neuropathy
  - phrenic nerve mononeuropathies, 17*t*, 618
  - phrenic neuropathies, 13–14
  - primary vasculitis and, 1065–1066
  - respiratory failure and, 12*t*, 14
  - restless legs syndrome and, 256
  - sensory
    - differential diagnosis of, 1062–1074
    - docetaxel and, 525
    - ixabepilone and, 525–526, 617, 617*t*
    - nelarabine and, 525
    - in rheumatoid arthritis, 896–897
    - in sarcoidosis, 876
  - sudomotor, 312
  - toxic
    - alcoholic, 634–635, 1072
    - arsenic, 654, 1073
    - lead, 653–654, 1073
    - organic solvents and, 652
    - organophosphate-induced, 657
    - pyridoxine-induced, 1072
  - uremic, 255–257, 1071
  - vasculitic, 501*t*, 515, 517, 901, 1058*t*, 1065–1068
- Neuropathy target esterase, 656
- Neurosarcoidosis, 847–848, 867–880
  - alternative treatments for, 883
  - brain imaging studies of, 878
  - brainstem auditory evoked potentials for, 878
  - cerebrospinal fluid analysis of, 848, 878
  - complications of, 871*t*
  - corticosteroids for, 883
  - cranial neuropathy in, 871, 880
  - definite, 879*t*
  - description of, 847, 867
  - diagnosis of, 877–879, 878*f*
  - diagnostic criteria for, 879*t*
  - diagnostic testing, 848
  - differential diagnosis of, 877–879
  - electromyography in, 878
  - encephalopathy-vasculopathy in, 874–875
  - endocrine disorders and, 873–874
  - evoked potentials for, 878
  - facial palsy, 712, 871
  - general supportive care for, 883
  - granulomatous inflammation of, 869*f*
  - hydrocephalus in, 873, 881
  - hypothalamic function affected by, 662, 873–874
  - immunosuppressants for, 882–883

  inflammation and, 869, 870*f*
  intracranial mass lesions, 874*f*
  intraparenchymal mass lesions, 874
  ischemic stroke caused by, 875
  magnetic resonance imaging of, 848, 878, 878*f*
  mass lesions, 874, 874*f*, 881
  meningeal disease in, 812*t*, 840*t*, 841*t*, 847–848, 872–873
  mortality caused by, 883
  myelopathy in, 875
  myopathy in, 876–877, 882
  nerve conduction studies in, 878
  neurologic manifestations of, 871–877, 1091
  neuropathy in, 875–876, 882
  noncaseating granulomas in, 869
  ocular motility disorders, 871–872
  olfactory nerve dysfunction, 871
  optic neuropathy, 871
  parenchymal disease, 873–875, 881–882
  pathology of, 869, 870*f*
  possible, 879*t*
  presentation, 847
  probable, 879*t*
  prognosis for, 883–884
  refractory, 882–883
  risk factors, 847
  seizures in, 875, 882
  somatosensory evoked potentials in, 878
  transient ischemic attack caused by, 875
  treatment, 848, 879–883
  visual evoked potentials in, 878
Neurosyphilis, 703–707, 711, 845
  clinical features of, 706–707, 845–846
  dementia and, 707
  diagnostic testing, 705–707, 846
  presentation, 845–846
  risk factors, 845
  treatment, 707, 846
Neurotoxic disorders, occupational
  arsenic, 654–655, 654*f*, 1073
  autonomic dysfunction and, 129
  carbamate pesticides, 656–658, 1075*t*
  description of, 647–649
  encephalopathies caused by
    acute, 648
    chronic, 648–649
  features suggestive of, 657*t*
  heavy metals, 652–656
  lead and, 652–654, 1073
  manganese, 655–656, 656*f*
  manifestations of, 648
  mercury, 655
  organic solvents, 651–652
  organochlorine insecticides, 658–659
  organophosphate pesticides, 656–658, 657*t*
  peripheral neuropathy caused by, 649. *See also individual disorders*
  pesticides and parkinsonism, 659
  pyrethroid insecticides, 658–659
  screening for, 649–650
Neurotoxicity syndrome
  immune effector cell therapy–associated neurotoxicity syndrome (ICANS), 459, 529, 801
Niacin, 236*t*
Niacin deficiency, 209–210, 245–246
  clinical manifestations, 246
  diagnosis, 246
  etiology, 246
  treatment, 246
Nicotinic receptors, in urothelium, 542–543
Nifurtimox-eflornithine combination therapy (NECT), 829
Nightmares, 934–935
Nimodipine, 108, 168, 769, 1041
Nipah virus, 743*t*
Nitrous oxide, 236*t*, 237, 604, 616, 644, 644*f*, 984, 986, 986*t*, 1036*t*, 1063*t*
  vitamin B_{12} deficiency and, 443–444
Nivolumab, 481, 482*t*, 529, 622
N-methyl-D-aspartate (NMDA) receptors. *See also* Anti-NMDAR syndrome
  activation of
    after cardiac arrest, 148
    in uremic encephalopathy, 252
  antagonist of, 1100
  dextromethorphan effects on, 643–644
  ventral respiratory groups mediated by, 4
N-methyl-D-aspartate antagonists, 643
Nocardia asteroides, 692–693
Nodding syndrome (NS), 836
Noise-induced hearing loss, 411
Nonarteritic ischemic optic neuropathy
  anterior, 419–420, 420*t*
  description of, 259, 420
  posterior, 420*t*
Nonbacterial endocarditis, systemic lupus erythematosus and, 887
Nonbacterial thrombotic endocarditis (NBTE), 77, 181*f*, 182, 793, 1091–1092
  and stroke, 181*f*, 182
Nonconvulsive seizures, 49, 971, 1012, 1094
Nonconvulsive status epilepticus, 253, 288, 526, 578, 606, 981, 995, 1014–1015, 1021, 1093–1094
Nondiabetic lumbosacral radiculoplexus neuropathy, 1061
Nonepileptic seizures (NESs), 330, 943, 986
Nonevaporative heat loss, 661
Non-Hodgkin lymphoma, 264–265, 453–454, 458*t*, 459, 481, 493, 495, 528, 891, 1080
Non–24-hour sleep–wake rhythm disorder (N24SWD), 931
Nonketotic hyperosmolar hyperglycemia, 1031
Nonketotic hyperosmolar syndrome, 303–304
Nonmyeloablative reduced intensity conditioning, 791
Non-necrotizing myelitis, 514
Nonrestorative sleep, 917
Nonshivering thermogenesis, 661, 664
Nonsteroidal anti-inflammatory drugs (NSAIDs), 267, 380, 463, 479, 523*t*, 536, 581, 604, 738, 799, 813*t*, 840*t*, 850, 889, 892, 897, 970, 986, 1036*t*, 1048–1049, 1048*t*, 1052, 1053*t*
  during lactation, 582
  during pregnancy, 581
Nonsystemic vasculitic neuropathy (NSVN), 899–900, 1065–1066
Non-vitamin K oral anticoagulants, 72, 79–80
Noonan syndrome, 54–55, 58
Norepinephrine
  level and infusion, for autonomic function evaluation, 138
  in multisystem atrophy, 130
  in pure autonomic failure, 130
Norepinephrine reuptake inhibitors, for cataplexy, 923
Norepinephrine transporter (NET), 131
NOTCH3 gene, 115
N-3-pridylmethyl-*N*-*p*-nitrophenyl urea, 129–130
NREM parasomnias, 933–934, 934*t*
N-terminal fragment B-type natriuretic peptide (NTproBNP), 70
Nucleic acid amplification test, 721

Nucleic acid-based amplification (NAA) techniques, 721
Nucleus paragigantocellularis, 560
Nucleus tractus solitarius, 126
Numb chin syndrome, 448, 483*t*
Nutritional disorders
  copper deficiency. *See* Copper, deficiency of
  diagnosis of, 236*t*
  folate deficiency, 238–240
  konzo, 248
  lathyrism, 247–248
  niacin deficiency, 246
  otoneurologic manifestations of, 411–412
  in pregnancy, 596
  pyridoxine deficiency. *See* Pyridoxine, deficiency of
  thiamine deficiency. *See* Thiamine deficiency
  treatment of, 236*t*
  vitamin A deficiency, 246–247
  vitamin B_{12} deficiency. *See* Vitamin B_{12} deficiency
  vitamin D deficiency, 247
  vitamin E deficiency, 241–242
Nutritional neuropathy
  copper deficiency, 240, 1072
  folate deficiency, 239
  vitamin B_1 deficiency, 243–244, 1071–1072. *See also* Korsakoff syndrome; Wernicke encephalopathy
  vitamin B_6 deficiency, 245, 1072
  vitamin B_{12} deficiency, 237, 1072
  vitamin E deficiency, 242, 1072
Nuvigil. *See* Armodafinil
Nystagmus, 431–433
  Brun, 432
  central vestibular, 432
  congenital, 432–433
  drug-induced, 615
  examination for, 431
  fusional maldevelopment, 433
  gaze-evoked, 431
  infantile, 432–433
  latent, 433
  monocular “shimmering”, 433
  pendular, 431–432
  peripheral vestibular, 432
  physiologic endgaze, 431
  see-saw, 432

O

Obesity
  Alzheimer disease and, 1100
  bariatric surgery for, 201–202, 235, 379–380
  Cushing disease and, 332, 334*t*, 339*t*
  and headache, 1047, 1051
  and heatstroke, 665
  and hypertension, 69, 103, 175
  and idiopathic intracranial hypertension, 422, 423*t*
  meralgia paresthetica and, 309
  narcolepsy and, 921
  and pseudopolycythemia, 456–457
  sleep apnea and, 924, 926
  vascular dementia and, 1100–1101
Obstetric management of maternal epilepsy, 580–581
Obstructive hydrocephalus, 384, 386, 590, 722, 808
Obstructive sleep apnea (OSA), 16–19, 71
  behavioral modifications for, 927
  cardiovascular disorders and, 915
  clinical evaluation of, 915, 925–926
  cognitive dysfunction secondary to, 18–19, 1104
  continuous positive airway pressure for, 926
  contributing factors, 288
  definition of, 924
  dementia and, 1100*t*, 1104
  diagnosis of, 924
  epidemiology, 924
  epilepsy and, 19, 936–937
  excessive daytime sleepiness and, 924
  headache secondary to, 19, 937, 1051
  home sleep studies and, 916
  hypoglossal nerve stimulation and, 927
  hypothyroidism and, 288
  idiopathic intracranial hypertension, 423
  kidney disease and, 261
  melatonin receptor agonists and, 919–920
  morbidity and mortality associated with, 915
  in multiple system atrophy, 1109
  narcolepsy and, 922–923
  oral appliances for, 927
  physiologic consequences of, 925
  polysomnography of, 925–926, 926*f*
  positive airway pressure for, 926
  predisposing factors, 924–925
  prevalence of, 924
  sex hormones and, 326–327
  surgery for, 926
  symptoms of, 924
  treatment of, 922–923, 926, 936–937
  vascular disorders and, 18
  weight loss for, 927
Obturator nerve
  anatomy of, 31*f*, 32
  injury of, during labor and delivery, 596
  palsy of, 310
Occlusive vascular disease, in pregnancy, 585–586
Ocrelizumab, 800
  during pregnancy, 593
Octreotide, 231, 332, 484, 523*t*
Ocular bobbing, 433
Ocular dipping, 433
Ocular dysmotility, 427
Ocular flutter, 433
Ocular misalignment, 424
Ocular syphilis, 355
Ocular tilt reaction, 427
Ocular toxoplasmosis (OT), 825, 827
Oculomasticatory myorhythmia, 207, 433
Oculomotor apraxia, 363, 467
Oculomotor nerve
  innervations by, 427–428, 434, 436
  lesions of, 310, 428, 451, 456, 526, 700, 903
OKT3 monoclonal antibody, 799
Olanzapine, 605*t*, 606, 611, 612*t*, 919*t*, 920, 981, 1014*t*, 1021, 1042, 1107
Olfactory nerve dysfunction, 761, 871
Oligodendrogliomas, 323
Olivopontocerebellar atrophy, 127, 129–130, 1101
Onchocerca volvulus, 836
Onchocerciasis, 618, 836
  ivermectin treatment of, 836
Onconeural antigens, 501
Oncospheres, 832
Ondansetron, 605*t*, 609, 966, 1027*t*, 1049, 1052
Ondine curse, 9. *See also* Congenital central hypoventilation syndrome

"On-off" phenomenon, 610
Open-heart surgery
  cardiopulmonary bypass for, 47
  phrenic nerve injury after, 45–46
Ophthalmoplegia. *See also individual ocular motor nerves*
  in cranial myeloma, 449–450
  internuclear, 207, 279, 425–426, 429–430, 443, 545, 615
  progressive external, 425*t*, 623
Opiates, 548*t*, 591–592, 608, 611, 641–643, 664, 666*t*, 967, 968*t*, 981, 988, 1036*t*, 1038, 1051
  hyperthermia and, 666*t*
Opioids
  bladder function and, 543
  dementia and, 987
  in diabetic neuropathy, 315, 972
  for diarrhea, 312
  Huntington disease and, 988
  for leptomeningeal metastases, 492
  and migraine, 581, 1048, 1052
  myoclonus and, 611
  mysathenia gravis and, 973–974
  neuromuscular disorders and, 971–972
  for pain, 311–312, 315, 981, 1115–1116, 1121
  in Parkinson disease, 987
  in premenstrual syndrome, 326
  for restless legs, 257–258
  seizures and, 971, 987–988, 1014*t*, 1021
  serotonin syndrome and, 613
Opportunistic infections
  HIV-related. *See also* Human immunodeficiency virus
    cryptococcal meningitis, 776*t*, 779
    cytomegalovirus encephalitis, 776*t*, 780
    diagnosis of, 776*t*, 777*f*
    overview of, 775–781
    primary CNS lymphoma, 776*t*, 778–779
    progressive multifocal leukoencephalopathy (PML), 776*t*, 780
    toxoplasmosis, 776*t*, 777–778, 778*f*
    tuberculous meningitis. *See* Tuberculous meningitis (TM)
  transplantation-related, 790
Opsoclonus-myoclonus, 362*t*, 433, 503*t*, 506*t*, 508–513, 658, 1034, 1037
Opsoclonus-myoclonus ataxia syndrome (OMAS), 512
Optic nerve
  anatomy of, 415, 417*f*
  atrophy of, 416–417, 417*f*
  compression of, 297, 421
  retrobulbar portion of, 418*f*
Optic nerve gliomas, 345
Optic neuritis, 513–514
  description of, 415–416
  drugs that cause, 615
  inflammatory demyelinating, 417–418, 418*f*
  multiple sclerosis and, 417–418
  neuromyelitis optica and, 418–419, 418*f*, 419*f*
  as postinfectious complication, 761
  postinfectious encephalomyelitis and, 761
  in pregnancy, 594
Optic Neuritis Treatment Trial, 417
Optic neuropathy, 415–422
  after bariatric surgery, 202
  Behçet disease, 356
  classification of, 416–417, 416*t*
  compressive, 421
  copper deficiency and, 210
  drug-induced, 614–615
  genetic, 421–422
  hemodialysis-related, 261
  inflammatory demyelinating optic neuritis, 417–418, 418*f*
  ischemic, 44–45, 259, 419–421, 420*t*
  Leber hereditary, 421–422
  nonarteritic anterior ischemic, 419–420, 420*t*
  paraneoplastic, 514–515
  radiation therapy and, 534
  renal disease and, 259
  in sarcoidosis, 871
  in thyroid disease, 297–298, 297*f*
  vitamin B_{12} deficiency and, 237, 443
Optical coherence tomography, 213, 416–418, 419*f*
Optimal supportive care (OSC), 480
Oral appliances for obstructive sleep apnea, 927
Oral contraceptives
  anticonvulsants effect on, 320–321, 581
  chorea and, 321–322, 591
  cigarette smoking and, 319
  depression and, 326, 608
  failure of, 320–321
  idiopathic intracranial hypertension, 604
  inherited thrombophilias and, 177
  ischemic stroke and, 319–320, 604–605
  migraine and, 318
  movement disorders and, 321–322, 591, 611, 1027*t*, 1028
  porphyria and, 325
  premenstrual syndrome and, 326
  retinopathy and, 614
  stroke risks, 174, 183, 319, 583, 585, 604–605
  subarachnoid hemorrhage and, 105, 320, 604–605
Orbital myositis, 425*t*, 426*t*
Orbital neoplasms, 431
Orbital syndrome, 482, 483*t*
Orbital trauma, 430–431
Organ transplantation. *See* Transplantation
Organic solvents, 129, 651–652
Organochlorine insecticides, 658–659
Organophosphate pesticides, 656–658, 657*t*
Orgasm
  physiology of, 560–561, 561*f*
  in spinal cord injury patients, 569
Orobuccal-lingual dyskinesia, 610, 1027–1028
Oropharyngeal dysphagia, 219, 226
Orthostatic hypotension. *See* Postural hypotension
Orthotopic liver transplantation, 214, 1071
Osborn wave, 670
Oscillopsia, 410, 431, 433, 509, 613, 676*t*
Osimertinib, 481, 482*t*, 492
Osler nodes, 67*t*, 348*t*, 350
Osler–Weber–Rendu syndrome (Hereditary hemorrhagic telangiectasia), 348*t*, 349
Osmotic demyelination syndrome, 261, 276, 336, 785, 794, 1090
Osmotic myelinolysis, 275–276. *See also* Central pontine myelinolysis
Osteitis fibrosa cystica, 337
Osteoarthritis, 384–385, 917*t*
Osteogenesis imperfecta
  characteristics of, 408–409
  otoneurologic manifestations of, 408, 409*f*
Osteomalacia, 202, 379–381, 1078
  causes of, 379*t*
  characteristics of, 378–380
  clinical features of, 380
  hypophosphatemic, 381, 500*t*
  myopathy
    description of, 202, 279

Osteomalacia (*Continued*)
    proximal, 380
  radiologic features of, 380–381
  rickets caused by, 380
  treatment of, 381
  vitamin D deficiency and, 247, 379–380, 1077
  weakness in, 380, 1078
Osteomyelitis
  brain abscess and, 693
  epidural abscess and, 98, 696–699
  fungal infection and, 807, 811
  HIV infection and, 407
  recreational drug use and, 645
  tuberculous, 388–389
  vertebral, 387–389, 388*f*, 955
Osteopetrosis, 381–384, 384*t*
  allogenic hematopoietic cell transplantation for, 383
  autosomal-recessive, 383
  definition of, 381–382
  inheritance of, 381, 382*t*
  malignant, 382–383
  metabolic abnormalities in, 383
  neuropathic autosomal-recessive, 383
  non-neurologic features of, 382
  otoneurologic manifestations of, 409
  radiographic features of, 382
  treatment of, 382–383
  varieties of, 382–383
Osteoporosis, 377–379
  characteristics of, 377–378
  and corticosteroids, 332, 883
  Cushing syndrome, 332, 334*t*
  fractures caused by, 378
  growth hormone deficiency and, 336–337, 378*t*
  hypopituitarism and, 336
  neurologic diseases associated with, 378*t*
  postmenopausal, 625
  preventive treatments for, 378–379
  sarcoidosis and, 883
  sex hormones and, 326
  treatment of, complications of, 379, 625
  vertebral fractures caused by, 378–379
  in Wilson disease, 212–213
Osteosarcoma, 385, 488
Osteosclerotic myeloma, 450, 501, 506*t*, 1064*t*, 1071
Otitis externa, 407
Otitis media
  brain abscess and, 695*t*
  differential diagnosis of, 399
  intracranial complications of, 399–400
  radiation-induced, 534
  serous, 407
  tuberculous, 406–407
  Wegener granulomatosis and, 407
Otogenic meningitis, 400
Otologic disease
  aging and, 412–413
  benign paroxysmal positional vertigo, 401, 403*f*
  central auditory processing disorder, 405
  central vestibular disorders, 404–405
  cerebellopontine angle disorders, 401
  eighth nerve lesions, 401
  labyrinthine disorders, 400–401
  Meniere disease, 400–401
  middle ear pathology, 399–400
  neurologic manifestations of, 399–405
  presbycusis, 412–413, 413*f*
  superior semicircular canal dehiscence syndrome, 401–402, 404*f*
  in systemic disease, 405–412
    bone diseases, 408–409
    connective tissue disease, 408
    drug-induced disorders, 410–411
    endocrine disorders, 408
    environmental disorders, 411
    immune-mediated disease, 407–408
    infection, 405–407
    metabolic disorders, 408
    neoplastic disease, 411–412
    neurocutaneous syndromes, 408
    nutritional disorders, 411
Otologic syphilis, 355
Otosyphilis, 406
Ototoxicity, drug-induced, 410–411, 613–614
Overactive (neurogenic) bladder, 543, 545–546, 548, 552–555, 572*t*
Overflow incontinence, 224–225, 228
Oxaliplatin, 522*t*, 523*t*, 527–528, 617
Oxamniquine, for schistosomiasis, 837
Oxcarbazepine, 255, 291, 315, 527, 566, 572*t*, 578–579, 581, 1009*t*, 1010*t*, 1011, 1052
Oxybutynin, 554, 783
Oxycodone, for restless legs syndrome, 932*t*
Oxytocin, 329, 333, 336*t*, 605*t*, 606, 620*t*, 1075*t*

P

Pacemaker, circadian, 931
Pacemakers, cardiac, 69, 133, 141, 141*t*, 598, 953–954
Pachymeningeal metastases, 484, 491
Pachymeningitis, 364, 840
Paclitaxel, 522*t*, 523*t*, 525, 617, 617*t*, 1064
Paget disease of bone, 384–387, 409
  back pain and, 385
  bisphosphonates for, 384
  cranial disease and, 384
  cranial nerve involvement, 384–385
  definition of, 384
  imaging of, 386*f*
  inclusion-body myopathy, Paget disease, and frontotemporal dementia, 386–387
  obstructive hydrocephalus and, 386
  otoneurologic manifestations of, 408, 409*f*
  serum alkaline phosphatase, 385
  skull osteosarcoma in, 385
  spine involvement in, 385
  treatment of, 386
Pain
  back. *See also individual disorders*
    in epidural spinal cord compression, 486
    nonsteroidal anti-inflammatory drugs for, 391
    in Paget disease of bone, 385
    in pregnancy, 594–595
    in tuberculous osteomyelitis, 389
    in vertebral osteomyelitis, 387
  breakthrough, 1115–1116
  during end of life, 1111–1112, 1115
  in leprosy, 736–738
  neuropathic. *See* Neuropathic pain
  opioids for, 311–312, 315, 981, 1115–1116, 1121
Painters' encephalopathy, 651
Palliative care, 1111–1122

Pancoast tumor, 435, 493–494
Pancreas, neuroendocrine tumors of, 340
Pancreatic encephalopathy
  clinical features of, 199–200
  definition of, 199–200
  diagnosis of, 200
  treatment of, 200
Pancreatic transplantation, 796
Pancreatitis, 849, 859
Pancuronium, 1001–1002
Pandysautonomias, 227
Pantothenate kinase-associated neurodegeneration, 446
Papillary fibroelastomas (PFE), 73
Papilledema, 18, 119–121, 262, 264, 289, 303, 349, 385, 393, 415, 416*t*, 422–423, 422*f*, 422*t*, 423*t*, 442, 447, 450, 456, 534, 583, 585–587, 604, 667, 685, 693, 719–720, 842, 871, 873, 970*t*, 1070
Paracoccidioides brasiliensis, 804*t*, 809
Paradoxical embolism, 73, 173
Paragonimiasis, 458*t*, 837
Paragonimus spp., 822*t*, 837
Paralysis
  periodic. *See* Periodic paralysis
  sleep, 921
Paramedian pontine reticular formation, 427
Parameningeal abscess, 97
Paranasal sinuses
  Aspergillus infection of, 790, 792, 810–811
  brain abscess from, 693–694, 695*t*
  chloromas in, 148
  fungal infection of, 805, 810
  in osteopetrosis, 383
  septic thromophlebitis and, 699
  sinusitis of
    subdural empyema and, 696
Paraneoplastic antibodies
  description of, 501–502, 506*t*, 1081, 1090
  in limbic encephalitis, 508
Paraneoplastic syndromes
  antibodies and, 505–506
  autonomic neuropathy, 129, 517
  basal ganglia encephalitis, 508–509
  brainstem encephalitis, 508–509
  of central nervous system, 505
  cerebellar degeneration
    antibodies associated with, 503*t*–504*t*, 506*t*, 510
    clinical findings, 509
    diagnosis of, 512
    immunosuppressive therapies for, 512
    intravenous immunoglobulin for, 512
    laboratory evaluation of, 509–511
    magnetic resonance imaging of, 509, 510*f*
    pathology of, 511
    Purkinje cells in, 511, 511*f*
    treatment of, 512
  cerebrospinal fluid findings, 501
  chorea in, 1031
  definition of, 499
  diagnosis of, 502–506, 502*t*
  dorsal root ganglion syndromes, 517
  dystonia in, 1031
  encephalomyelitis, 508
  hypothalamic dysfunction, 508
  incidence of, 499–501
  Lambert–Eaton myasthenic syndrome, 12*t*, 15, 499–501, 501*t*, 504*t*, 506*t*, 517–519, 997, 997*t*, 1075–1076
  like motor neuron disease, 514
  limbic encephalitis, 507–508, 1015
  list of, 500*t*
  muscle syndromes, 519–520, 1081
  myasthenia gravis. *See* Myasthenia gravis (MG)
  myoclonus and, 1037
  neurologic disability caused by, 504–505
  neuromuscular junction syndromes, 517–519
  non-necrotizing myelitis, 514
  non-neurologic, 500*t*
  opsoclonus-myoclonus, 506*t*, 512–513
  optic neuropathy, 513–514
  parkinsonism and, 1044–1045
  pathogenesis of, 501–502
  of peripheral nerve, 500–501, 515–517, 1071
  retinopathy, 513
  sensory neuronopathy, 515–516, 516*f*, 1060
  spinal cord syndromes, 514–515
  stiff-person syndrome, 501*t*, 506*t*, 515
  subacute necrotizing myelopathy, 514
  treatment of, 506, 506*t*
  visual loss caused by, 513–514
Paraplegia, pregnancy in patients with, 594
Paraproteinemias, 452–453
Paraquat, 659
Parasellar syndrome, 483*t*
Parasitic infections. *See also individual disorders*
  in post-transplantation period, 790
Parasomnias
  arousal disorders, 934
  confusional arousals, 933
  definition of, 933
  epilepsy versus, 936–937
  exploding head syndrome, 935
  forensic implications of, 935
  nightmares, 934–935
  NREM, 933–934, 934*t*
  REM, 934–935
  sexsomnia, 935
  sleep terrors, 933–934
  sleep-related eating disorders, 934*t*, 935
  sleepwalking, 933
  treatment of, 934*t*
Parathyroid adenomas, 279, 337
Parathyroid glands, 337–338
  anatomy of, 337
  hyperparathyroidism, 337
  hypoparathyroidism, 338
Parathyroid hormone
  uremic encephalopathy and, 252
Paravahlkampfia species, 830
Paraventricular nucleus of hypothalamus, 158
Parinaud dorsal midbrain syndrome, 425*t*, 427, 434
Parkinson disease
  anesthesia in, 987
  aspiration in, 1105
  carriers of *GBA1* mutations with, 467
  constipation in, 226, 1109
  deep brain stimulation for, 966, 987, 1045–1046
  dementia in, 1101
  depression and, 1108
  dysphagia and, 219
  excessive daytime sleepiness and, 1109
  falls and, 1108
  herbicides and, 659
  lower urinary tract symptoms in, 545

Parkinson disease (*Continued*)
  and movement disorders in pregnancy, 592
  overactive bladder in, 545, 1109–1110
  perioperative care, 965–966
  pesticides and, 659
  postural hypotension in, 127, 1105*t*
  in pregnancy, 592
  respiratory dysfunction in, 11
  sexual dysfunction in, 566–567
  sleep disorders in, 936, 1109
  succinylcholine and, 987
  systemic complications of, 1105*t*
  urinary incontinence in, 1109–1110
Parkinsonian crisis, 965–966
Parkinsonism
  AIDS-associated, 1044
  autoimmune disorders and, 1044–1045
  bone marrow transplantation and, 1042
  cirrhosis-related, 192–193
  constipation in, 226
  dementia and, 1101
  diagnosis of, 1045
  drug-induced, 322, 611–612, 1042
  dysautonomia and, 127, 129–130, 966, 1105*t*
  estrogen therapy and, 322
  falls and, 1108
  functional, 942*t*, 943
  gastrointestinal dysfunction with, 226
  head trauma and, 1045
  heroin and, 642*f*
  HIV and, 1044
  infections and, 1043–1044
  manganese-induced, 260, 656, 1042
  metabolic disorders and, 1043
  methanol poisoning and, 1042–1043
  methylphenyl tetrahydropyridine, 659
  paraneoplastic disorders and, 1044–1045
  rest tremor and, 1038
  secondary, 1045
  subdural hematoma and, 1042, 1045
  synucleinopathies and, 1101
  systemic lupus erythematosus and, 1044–1045
  toxins and, 1042–1043
  trauma and, 1045
  treatment of, 1045–1046
  tuberculous meningitis and, 1044
  vascular causes of, 1041–1042
Paroxetine, 575, 612*t*, 769, 934, 934*t*, 1026
Paroxysmal atrial fibrillation, 66–67, 69. *See also* Atrial fibrillation (AF)
Paroxysmal choreoathetosis, 1031
Paroxysmal nocturnal hemoglobinuria, 445
Paroxysmal supraventricular tachycardia, 71, 83
Paroxysmal sympathetic hyperactivity (PSH), 166
Parry–Romberg syndrome, 1016
Parsonage–Turner syndrome, 1061
Partial thromboplastin time (PTT), 175*t*, 182, 462, 467, 887
Particle repositioning maneuver, 401, 403*f*
Passive external rewarming, for hypothermia, 670
Patent foramen ovale (PFO), 68–69, 73
  description of, 474
  and migraine, 1048–1049
  stroke caused by, 80–81, 173–175
PCSK9 antibodies, 172
Pellagra, 209–210, 245–246, 364, 366*t*, 631, 1034
Pelvic floor electromyography, 551
Pelvic neurophysiology, 551–553
Pembrolizumab, 460, 481, 529, 620, 622
Pemoline, 611, 1026, 1027*t*
Pendred syndrome, 408
Pendular nystagmus, 431–432
Penicillamine, 214, 245, 592, 614–615, 617*t*, 618–621, 620*t*, 624, 898, 1026, 1075*t*, 1076
Penicillium marneffei, 809
Penilo-cavernosus reflex, 552
Penis. *See also* Sexual dysfunction
  blood supply to, 34
  corpora cavernosa of, 560
  erection of, 34, 560
  examination of, 563
  investigation of arousal on, 563–564
  investigation of neurologic function, and, 564–565
  nerve supply of, 33–34, 33*f*, 34*f*, 558–562, 559*f*
  pudendal somatosensory evoked potentials, 552–553
  sexual excitement effects on, 34, 558–559
Pentamidine, 831, 1083
Percutaneous endoscopic gastrostomy, 225, 1121
Percutaneous enteral feeding, 1105–1106
Percutaneous tibial nerve stimulation, 555
Perhexiline, 129, 612, 617*t*, 618, 624
Perimenopausal migraine, 318
Perineurial granulomas, in sarcoidosis, 875–876
Periodic alternating nystagmus, 432
Periodic hyperthermia, 664
Periodic limb movements, 327, 915, 933
Periodic paralysis
  hyperkalemic, 278, 339, 1058*t*
  hypokalemic (thyrotoxic), 293–294, 624, 1058*t*, 1078
  Na^+,K^+-ATPase pump and, 294
  pathophysiology of, 294
  thyrotoxic, 1078
  treatment of, 294–295
  weakness associated with, 293
Perioperative period
  anticoagulation in, 976
  cognitive dysfunction, 981–982
  coma in, 979–981
  cranial nerve palsies, 985
  delirium, 967–969, 968*t*, 981
  dementia, 969
  headache, 969–970, 970*t*, 986
  hearing loss, 984–985
  intracranial hypotension, 970
  motor neuron disease, 972
  movement disorders, 966–967
  multiple sclerosis care, 967
  myasthenia gravis, 973
  myopathies, 972–973
  neuroleptic malignant syndrome, 985. *See also* Neuroleptic malignant syndrome
  neuropathy, 972, 983, 983*f*, 984*f*
  paraparesis, 983
  Parkinson disease care, 966
  seizures, 970–971, 985–986
  serotonin syndrome, 985
  stroke and, 975
  transient neurologic symptoms, 984
  visual loss, 984
Peripartum cardiomyopathy, 584
Peripheral chemoreceptors, 4
Peripheral nerve disorders in pregnancy, 595–597
  Bell palsy, 596

  - entrapment neuropathies, 595–596
  - polyneuropathies, 596–597
  - traumatic mononeuropathies, 596
- Peripheral nerve(s)
  - disorders of. *See* Neuropathy; Peripheral neuropathy; Polyneuropathy; *specific disorders*
  - hyperexcitability, 519
  - injury, 49. *See also* Peripheral neuropathy; Polyneuropathy; *specific disorders*
    - during transplantation procedure, 795–796
  - metastases to, 495–496
  - paraneoplastic syndromes of, 500–501, 501*t*, 515–517, 1071
  - radiation injury to, 534–535
- Peripheral nervous system
  - Behçet disease manifestations of, 906
  - calcineurin inhibitors and, 797
  - complications after CABG, 45–46
  - neuroborreliosis manifestations of, 711–712, 712*t*
  - polyarteritis nodosa manifestations of, 900
  - rheumatoid arthritis manifestations of, 895–897
  - Sjögren syndrome manifestations of, 891–892
  - systemic lupus erythematosus manifestations in, 889
  - systemic vasculitis manifestations of, 902
  - temporal arteritis manifestations of, 903
- Peripheral neuropathy, 202, 1063*t*. *See also* Neuropathy; Polyneuropathy; *specific disorders*
  - antimicrobial agents and, 618
  - antineoplastic drugs and, 617–618
  - antirheumatic drugs and, 618
  - aortic disease and, 31–35
  - ara-C and, 524–525
  - arsenic and, 654
  - cardiovascular drugs and, 618
  - celiac disease and, 204
  - chemotherapeutic agents and, 523*t*, 524–527, 529, 616–619
  - cholesterol-lowering drugs and, 618–619
  - cisplatin and, 527
  - cutaneous manifestations of, 365–369, 366*t*
  - differential diagnosis of, 1062–1074
  - disulfiram and, 619
  - drugs that cause, 616–619
  - Fabry disease, 1063*t*, 1073
  - HIV-associated, 781–782
  - hyperthyroidism and, 295
  - hypnotics and, 619
  - hypothyroidism and, 291
  - inflammatory bowel disease and, 204–205
  - large-fiber sensory loss with, 1063*t*
  - lead, 653–654
  - leprosy and, 365–367, 730–733, 735
  - levodopa and, 619
  - lower urinary tract dysfunction and, 546–547
  - mercury and, 655
  - microvasculitis and, 517
  - myelomatosis and, 450
  - occupational neurotoxin exposure as cause of, 649
  - organic solvents and, 651–652
  - oxaliplatin and, 527–528
  - paraneoplastic, 455, 500–501, 515–517, 1071
  - phenytoin and, 619
  - psychotropic drugs and, 619
  - pyridoxine and, 619
  - sarcoidosis and, 875–876, 882
  - Sjögren syndrome and, 891
  - small-fiber sensory loss with, 1063*t*
- Peripheral neuropathy, gut dysmotility and
  - acute, 228–231
  - amyloid neuropathy, 229–230
  - autoimmune neuropathies, 230–231
  - chronic, 228–231
  - chronic sensory and autonomic neuropathy, 230
  - diabetes mellitus, 228–229
  - human immunodeficiency virus (HIV) infection, 230
  - neurofibromatosis, 230
  - paraneoplastic neuropathy, 229
  - porphyria, 230
- Peripheral vestibular nystagmus, 431
- Periventricular white matter disease, 56, 114–115, 114*f*
- Pernicious anemia, 237–238, 443, 644, 1072
- Perry syndrome, 11
- Persistent postural-perceptual dizziness, 943–944
- Persistent vegetative state, 149, 1033, 1097–1098, 1117–1119
- Pertussis vaccine, 854, 860–861
- Pesticides, 656
- PHACE syndrome, 58
- Phaeohyphomycosis, 811
- Phakomatoses, 343–344, 360
- Pharyngoesophageal motility studies, 219–221
- Pharyngolaryngeal dysesthesia syndrome, 527–528
- Phencyclidine, 605*t*, 606, 643, 1020
- Phenobarbital, 132, 247, 255, 321–322, 479, 566, 578–581, 609, 611, 936, 970–971, 1009*t*, 1011–1012, 1017–1019, 1022, 1034, 1037
- Phenolic glycolipid 1 (PGL-1), 729
- Phenothiazines, 221, 605*t*, 606–612, 614, 616, 620, 669, 1048*t*, 1075*t*
  - hyperthermia and, 666*t*
  - hypothermia and, 667*t*
- Phenylephrine, 141*t*, 142*t*, 144, 168, 436
- Phenylketonuria, 239, 364, 367*t*, 590–591
- Phenylpropanolamine, 574, 605–606, 611
- Phenytoin, 247, 255, 279, 291, 320–321, 462, 479, 495, 506*t*, 519, 566, 572*t*, 578–581, 599, 606, 609, 611–612, 614–615, 619, 620*t*, 622, 759, 786–787, 936, 970–971, 1009*t*, 1011–1012, 1016–1019, 1022, 1026–1027, 1036*t*, 1039*t*, 1064*t*, 1073, 1075*t*
  - fetal malformations caused by, 579
  - hyperglycemia and, 1019
  - peripheral neuropathy caused by, 619
  - pharmacokinetics of, 1009*t*
  - and thyroid disease, 291, 1019
  - uremic convulsions and, 255
- Pheochromocytoma, 125, 158, 269, 339–340, 456, 662*t*, 665, 668, 1040, 1049
- Phosphodiesterase-5 inhibitors, 573
- Phosphoinositide (PI) 3-kinase (PI3K), 314
- Phospholipase A, 199
- Photoplethysmography, 135, 137–138, 138*f*
- *PHOX2B* gene, 6, 9
- Phrenic nerve/neuropathy
  - adalimumab and, 618
  - bilateral injury of, 45–46
  - cardiac surgery-induced injury of, 45–46, 794–795
  - conduction studies of, 14–15, 1002
  - critical illness polyneuropathy and, 14, 998, 1000, 1002–1003
  - hiccup and, 10
  - metastatic involvement of, 493, 495
  - palsy of, imaging and, 7
  - plexopathy, brachial, and, 1061
  - respiratory failure and, 12*t*, 13–14
  - and transplantation procedures, 795–796
  - unilateral injury of, 45–46

Physiologic endgaze nystagmus, 431
Physostigmine, 980, 1036*t*
Phytanic acid, 364, 1074
Pierson syndrome, 260
Pigmentary retinopathy, 614
Pimavanserin, 1107
Pitolisant, 922*t*, 923
Pittsburgh Sleep Quality Index, 917–918
Pituitary adenomas
  clinically nonfunctioning, 333
  description of, 328–329, 329*f*
  diagnosis of, 334*t*
  management of, 334*t*
  in pregnancy, 582
Pituitary apoplexy, 44, 330*t*, 333
Pituitary gland, 327–337
  adenomas of. *See* Pituitary adenomas
  anterior
    adrenocorticotropic hormone secretion by, 332
    amenorrhea-galactorrhea, 330–331
    Cushing disease, 332
    embryology of, 327–328
    growth hormone secretion by, 331–332
    hormones produced by, 327–328, 328*t*
    hyperprolactinemia, 330, 331*t*
    prolactin secretion by, 330–331
    thyroid-stimulating hormone, 332–333
  apoplexy of, 44, 330*t*, 333
  embryology of, 327–328
  hemorrhage of, in pregnancy, 586
  hormones produced by, 330*t*
  infarction of, in pregnancy, 586
  magnetic resonance imaging of, 329–330
  parasellar lesions, 328–330
  posterior
    antidiuretic hormone, 335–336
    diabetes insipidus, 334–335, 335*t*
    embryology of, 328
    hypopituitarism, 336–337, 337*t*
    oxytocin, 333–334
    syndrome of inappropriate antidiuretic hormone, 335–336, 336*t*
  sellar region of
    anatomy of, 328
    lesions in, 328–330, 330*t*
Pituitary infarction or hemorrhage in pregnancy, 586
Pituitary region tumors, 1052
Plague, bubonic, 353*t*
Plasmapheresis, 761, 889–890. *See also indiividual disorders*
  for acute disseminated encephalomyelitis, 763
  for chronic inflammatory demyelinating neuropathy, 1070
  for cryoglobulinemia-related neurologic complications, 178
  for Guillain–Barré syndrome, 128, 260, 597, 1069–1070
  for Hashimoto encephalopathy, 301
  for MGUS, 453, 1070
  for myasthenia gravis, 597
  for myelomatosis or macroglobulinemia, 463
  for paraneoplastic sensory neuronopathy, 1060
  in pregnancy, 597
  for Refsum disease, 364, 1074
  for stiff-person syndrome, 515
  for systemic lupus erythematosus, 889–890
  for thrombotic thrombocytopenic purpura, 358
  for thyroid storm, 299
Plasminogen deficiency, 362*t*
Plasmodium falciparum, 821–823, 822*t*, 1040
Plasmodium falciparum erythrocyte membrane protein, 1, 823
Platelet function disorders, 463
Platelet-derived growth factor receptor a [PDGFRa], 218
Platinums, neurologic complications of, 527–528
Plexiform neurofibromas, 344–345
Plexopathy, 493–495, 534–535, 1061–1062. *See also* Brachial plexopathy
Plexopathy, brachial. *See* Brachial plexopathy
Plexus lesions, in pregnancy, 595
Plexus lesions, metastatic, 493–495
Pneumococcal meningitis
  antimicrobial therapy for, 688–689, 689*t*
  vaccination against, 692
Podophyllin, 606, 617*t*, 618
POEMS syndrome, 327, 366*t*, 367*t*, 450, 1064*t*, 1071
Poliomyelitis, 12*t*, 13, 17*t*, 589, 743*t*, 856*t*, 863, 1058–1059
  acute respiratory failure and, 13
  in pregnancy, 589
  vaccine for, 863
Polioviruses, 742
Polyarteritis nodosa, 210, 368, 408, 458*t*, 900, 1030–1031, 1052, 1066, 1092
Polycystic kidney disease, 105, 269–270, 795
Polycythemia, 59, 349, 455–456, 583, 591, 1025, 1092
Polycythemic chorea, 591, 1025
Polymerase chain reaction (PCR), 406, 712, 730, 734, 746, 775, 776*t*, 806, 827, 841, 1059
Polymyalgia rheumatica (PMR), 902–904, 1081
  and giant-cell arteritis, 902–904
    central nervous system disease, 903
    peripheral nervous system disease, 903
    systemic disease, 902–903
    treatment, 903–904
  hypothyroidism and, 291
Polymyositis, 15, 519, 621–622, 897–898, 1079–1080
  comorbidities, 1080
  corticosteroids for, 1080
  cutaneous manifestations of, 1079
  dermatomyositis and, 369
  drug-induced, 621–622
  dysphagia and, 219
  eosinophlic, 457
  epidemiology of, 1079
  gastroparesis in, 231
  hepatitis C infection and, 211
  HIV and, 782, 1078
  incidence of, 1079
  interstitial lung disease in, 1079–1080
  and malignancy, 519
  and rheumatoid arthritis, 897
Polymyxins, 619–620
Polyneuropathy, 1068–1074. *See also* Neuropathy; Peripheral neuropathy; *specific disorders*
  amyloidosis and, 1071
  autonomic involvement in, 127–128
  chronic inflammatory demyelinating (CIDP), 128, 205, 306, 450, 452, 460, 506*t*, 571, 597, 618–619, 634, 781, 797, 841, 856*t*, 972, 1002, 1041, 1063*t*, 1064*t*, 1067, 1070
  critical illness. *See* Critical illness polyneuropathy (CIP)
  diabetic. *See* Diabetic polyneuropathy
  endocrine, 1068
  Fabry disease and, 1063*t*, 1073
  infectious, 1069
  ischemic neuropathy, 32–33
  monoclonal gammopathy of undetermined significance, 1070
  organophosphates and, 647, 657–658

  postural hypotension associated with, 128
  in pregnancy, 595–597
  sarcoidosis and, 875–876, 882
  systemic lupus erythematosus and, 889
  uremic, 255–257, 1071
Polysomnography
  of hypopnea/apnea, 924–926, 926*f*
  of idiopathic hypersomnias, 923
  of insomnia, 918
  of narcolepsy, 921–922
  of obstructive sleep apnea, 925–926, 926*f*
  pulmonary function evaluations using, 7
  of REM sleep behavior disorder, 935
  of sleep disorders, 915–916
Pomalidomide, 617
Pompe disease, 15–16
Pontine micturition area, 541–542, 545
Porphyria
  acute intermittent, 325–326, 1017
  autonomic involvement, 128
  characteristics of, 325, 1073–1074
  exacerbation of, during pregnancy, 597
  gut dysmotility and, 223*t*, 230
  hepatic, 1016–1017, 1074
  neurocutaneous manifestations of, 349, 357*t*, 366*t*
  peripheral nerve dysfunction, 210–211, 997*t*, 1063*t*, 1065*t*
  pregnancy and, 597
  seizures in, 1016–1017
  sex hormones and, 326
  types of, 1073–1074
  variegate, 358–359, 1017, 1040
Portosystemic encephalopathy (PSE) syndrome test, 194
Portosystemic hepatic encephalopathy score (PHES), 194, 195*f*
Positive airway pressure
  description of, 916
  for multiple system atrophy, 1109
  for obstructive sleep apnea, 926
Post-arrest syndrome, 147
Postconcussion syndrome, 673. *See also* Concussion/mild traumatic brain injury (mTBI)
Postdural puncture headache, 956, 970, 986*t*, 1050
Postencephalitic parkinsonism, 1044–1045
Posterior ischemic optic neuropathy, 44–45, 420–421, 984
Posterior pial arterial plexus, 23–24, 24*f*, 27
Posterior reversible encephalopathy syndrome (PRES), 121, 253, 254*f*, 259–261, 279, 356, 416*t*, 466, 528, 599, 600*f*, 615, 787*f*
  bevacizumab and, 528
  calcineurin inhibitors and, 797
  cerebral imaging studies of, 253
  chemotherapy, intrathecal, and, 530
  computed tomography of, 254*f*
  cyclosporine and, 121, 606, 607*f*
  description of, 259–260, 279, 356, 466
  eclampsia and, 121, 416*t*, 599, 600*f*
  hypercalcemia and, 279
  hypertensive encephalopathy as. *See* Hypertensive encephalopathy
  immunosuppressive agents that cause, 121, 259–260
  nephrotic syndrome and, 259–260
  postoperative delirium and, 981
  systemic lupus erythematosus and, 356, 888
  in thrombotic thrombocytopenic purpura, 466
  uremic encephalopathy and, 252
Posterior root ganglia disorders, 495, 501*t*, 706, 1060–1061, 1060*t*, 1072
Posterior spinal artery
  anatomy of, 23–24, 24*f*
  syndrome of, 27–28
Postherpetic neuralgia, 743*t*, 752, 1061
Posthyperventilation apnea, 9
Postictal arrhythmias, 165–166
Postictal coma, 165–166
Postinfectious encephalomyelitis, 761–762, 762*f*, 763*t*
Post-lumbar puncture headaches, 956, 970, 986*t*, 1050
Postoperative cognitive dysfunction, 981–982
Postoperative stereotactic radiosurgery, 481
Postpartum depression, 326
Postpartum period
  cerebral angiopathy in, 584
  hemolytic-uremic syndrome in, 599–600
Postpartum psychosis, 326
Postpolio syndrome, 17, 226, 988, 1058–1059
Postpump chorea, 1025
Postsympathectomy neuralgia
  aortic disease as cause of, 34
  definition of, 34
Post-transplant lymphoproliferative disorder (PTLD), 788, 791, 798*t*
Post-transplantation period. *See also* Transplantation
  central nervous system (CNS) infection, 787–790
  cerebrovascular complications in, 787
  encephalopathy in, 785–786
  seizures in, 786–787
Postural changes in heart rate, 134–135. *See also* Postural orthostatic tachycardia syndrome (POTS)
Postural hypotension, 123, 224
  age-related, 125–126
  autonomic function evaluation, 133–140
    blood pressure, postural change in, 134
      tilt-table testing, 134
    cardiovascular responses, 137
    cold pressor test, 138
    digital blood flow, 137–138, 138*f*
    heart rate, postural change in, 134–135
    plasma norepinephrine level and infusion, 138
    pupillary responses, 140
    radiologic studies, 140
    sweat tests, 139–140, 139*f*, 140*f*
    tyramine response, 139
    Valsalva maneuver, 135–137, 136*f*
  cardiovascular disorders that cause, 124–125
  definition of, 124
  dementia and, 1108–1109
  desmopressin for, 554
  diffuse Lewy body disease and, 127
  dihydroergotamine for, 144
  dihydroxyphenylserine (Droxidopa) for, 145
  drugs that cause, 125, 616
  effective blood volume alterations as cause of, 125
  endocrine disorders that cause, 125
  fludrocortisone for, 142–143
  head-up tilt for, 142
  heart and blood vessels, autonomic regulation of, 126
  metabolic disorders that cause, 125
  midrodrine for, 143
  neurologic causes of, 127–132
    botulism, 130
    brainstem lesions, 127
    central lesions, 127
    Holmes–Adie syndrome, 130
    postural orthostatic tachycardia syndrome, 131–132

- Postural hypotension (*Continued*)
    - primary degeneration of the autonomic nervous system, 129–130
    - root and peripheral nerve lesions, 127–129
        - hereditary disorders, 127–128
        - iatrogenic disorders, 129
        - infectious, inflammatory, and immune-mediated disorders, 128–129
        - metabolic disorders, 128
    - spinal cord injury, 127
    - toxic exposures, 129
  - non-neurologic causes of, 124–126
  - patient management of, 140–145, 142*t*, 143*f*
    - treatment of, 141–145
        - nonpharmacologic measures, 141–142
        - pharmacologic treatment, 142–145
  - physiology of, 124
  - postural adjustment inadequacies as cause of, 125
  - prostaglandin synthetase inhibitors for, 142–143
  - pyridostigmine for, 144
  - sympathomimetic drugs for, 144
  - syncope caused by, 126, 132
  - treatment of, 142*t*, 143*f*
  - vasopressin for, 144
  - vitamin B_{12} deficiency and, 237
- Postural myoclonus, 1037
- Postural orthostatic tachycardia syndrome (POTS), 131–132, 141, 311
  - gut dysmotility and, 227
- Potassium
  - disturbances of, 277–278
  - hyperkalemia, 278
  - hypokalemia, 277–278
  - restriction, in chronic kidney disease, 256
- Potassium channel mutations and periodic paralysis, 294
- Potassium-related myopathies, 623
- Powassan virus, 746, 754–755
- Pralidoxime, 657
- Pramipexole
  - and chorea, 1027*t*
  - and daytime sleepiness, 1109
  - for restless legs syndrome, 931–932, 932*t*
  - for sleep-related eating disorders, 934*t*
- Praziquantel, 833, 847
  - for cysticercosis, 833, 847
  - for paragonimiasis, 837
  - for schistosomiasis, 837
- Prazosin, for parasomnias, 934*t*, 935
- Pre-Bötzinger complex, 4
- Prednisone. *See* Corticosteroids; *specific diseases*
- Pre-eclampsia, 174, 599–600. *See also* Eclampsia
- Pregabalin, 255, 315, 572*t*, 575, 591, 608, 612, 752, 781, 932, 932*t*, 1008, 1010*t*, 1017–1019, 1041
- Pregnancy
  - in AIDS mothers, 589
  - alemtuzumab during, 594
  - amitriptyline during, 582
  - amniotic fluid embolism in, 584
  - anticoagulation during, 584
  - anticonvulsant drug treatment during, 580
  - antiparkinsonian medication during, 592
  - antiphospholipid antibodies in, 584
  - Bell palsy in, 596
  - β-interferon therapy during, 593
  - brachial plexopathy in, 595
  - carpal tunnel syndrome in, 595, 1064–1065
  - cerebral arteriovenous malformation in, 586–587, 586*f*
  - cerebrovascular disease in, 583–587
  - chorea gravidarum in, 321–322, 591, 1028
  - chronic inflammatory demyelinating polyneuropathy (CIDP) in, 597
  - cladribine during, 594
  - common fibular nerve injury in, 596
  - congenital toxoplasmosis and, 590, 825–826
  - cytomegalovirus infection in, 590
  - depression after, 326
  - dimethyl fumarate during, 593
  - disseminated intravascular coagulation in, 586
  - dural arteriovenous fistulas in, 587–588, 588*f*
  - dystonia in, 592
  - eclampsia in, 599–600, 600*f*
  - entrapment neuropathies in, 596
  - epilepsy in, 321, 578–579
  - essential tremor, 592
  - fingolimod during, 593
  - folate supplementation during, 580
  - glatiramer acetate during, 593
  - Guillain–Barré syndrome in, 596–597
  - hemostatic changes in, 468–469
  - herpes simplex virus infection in, 590
  - human T-cell leukemia virus, type I exposure, 589
  - hypercoagulability in, 583–584
  - hypertensive disorders of, 584
  - idiopathic intracranial hypertension in, 583
  - immunosuppression in, 324
  - infections in, 588–590
  - intracranial hemorrhage in, 587
  - intracranial tumors in, 582
  - intracranial venous thrombosis in, 585, 586*f*
  - ischemic stroke in, 584
  - *Listeria monocytogenes* infection during, 590
  - low back pain in, 594–595
  - lumbar disc prolapse during, 594–595
  - lumbosacral plexus lesions in, 595
  - maternal epilepsy in, 578–581
  - maternal rubella in, 590
  - maternal syphilis in, 590
  - memantine during, 582
  - meningiomas in, 323, 582
  - meralgia paresthetica in, 309, 595–596
  - migraine in, 581–582
  - mononeuropathies during, 596
  - movement disorders in, 591–592
  - multiple sclerosis in, 324, 592–594
  - myasthenia gravis in, 597–598
  - myotonic dystrophy in, 598–599
  - natalizumab during, 593
  - nervous system infections in, 588–590
  - nonsteroidal anti-inflammatory drugs during, 581–582
  - nutritional deficiency in, 596
  - occlusive arterial disease in, 583–585
  - occlusive venous disease in, 585–586, 585*f*
  - ocrelizumab during, 593
  - optic neuritis in, 594
  - in paraplegic patients, 594
  - Parkinson disease in, 592
  - peripartum cardiomyopathy in, 584
  - peripheral nerve disorders in, 595–597
  - phenylketonuria screenings, 590–591
  - pituitary adenoma enlargement in, 582
  - pituitary infarction or hemorrhage in, 586
  - plexus lesions in, 595

  poliomyelitis susceptibility during, 589
  polyneuropathies in, 596–597
  porphyria exacerbation during, 597
  pre-eclampsia in, 599–600
  propranolol during, 582, 592
  radiation therapy in, 582
  restless legs syndrome in, 591–592
  retroviral infections, 589
  root lesions in, 594–595
  sciatic nerve injury in, 596
  spinal arteriovenous fistulas in, 587–588
  spinal cord ischemia in, 24–25
  statin drugs during, 584–585
  status epilepticus in, 578
  status migrainosus in, 318
  stroke risks in, 174–175, 583
  subarachnoid hemorrhage, 586*f*, 587
  sumatriptan during, 581–582
  teriflunomide during, 593
  tetanus in, 589–590
  thrombotic thrombocytopenic purpura in, 599–600
  topiramate during, 582
  Tourette syndrome, 592
  toxic disorders in, 591–592
  toxoplasmosis in, 827
  transient ischemic attacks in, 584
  traumatic mononeuropathies in, 596
  traumatic paraplegia during, 594
  tuberculous meningitis in, 590
  tumors in, 582–583
  valproic acid during, 578–580, 582
  venous thrombosis in, 585, 585*f*
  vitamin B_{12} deficiency in, 590
  Wilson disease in, 592
Premenstrual syndrome
  neuropsychiatric symptoms of, 326
  treatment of, 326
Preoptic anterior hypothalamus, 662
Presbycusis, 412–413, 413*f*
Primary aldosteronism, 338
Primary amebic meningoencephalitis (PAM), 829–831, 830*f*
Primary amyloidosis, 127, 449, 1071
Primary angiitis, of the central nervous system, 898
Primary biliary cirrhosis, 210–211, 306*t*, 793, 890
Primary central nervous system vasculitis (PCNSV), 848–849, 898–899
Primary CNS lymphoma, 265–266, 266*f*, 454, 478, 496, 776*t*, 777–779, 790, 1091
Primary neuritic leprosy (PNL), 730, 732
Primary vasculitis of the peripheral nervous system, 899–900
  nonsystemic vasculitic neuropathy (NSVN), 899–900
Primidone, 255, 320–321, 566, 578, 580–581, 592, 612, 971, 1009*t*, 1033, 1036*t*, 1038, 1041
Prion diseases, 226, 759–760, 864, 1029*t*, 1044
Prochlorperazine, 610, 612*t*, 1049
Procollagen-1N-propeptide, in Paget disease, 384
Programmed cell death protein, 1, 529, 800
Progressive encephalomyelitis with rigidity and myoclonus (PERM), 515
Progressive external ophthalmoplegia, chronic, 425*t*, 623
Progressive multifocal leukoencephalopathy (PML), 267, 269*f*, 451, 500*t*, 523, 606, 741, 757–758, 758*f*, 772, 775–777, 776*t*, 780, 789, 789*f*, 847, 1018, 1030, 1044, 1091
  diagnosis of, 757
  fludarabine and, 523
  in HIV-infected patients, 775–777, 776*t*, 780
  JC virus and, 741–742, 757, 780, 1043–1044, 1091
  magnetic resonance imaging of, 757, 758*f*
  remission of, 780
  treatment of, 757–758
Progressive respiratory muscle weakness, 14
Progressive supranuclear palsy, 127, 226, 323, 425*t*, 447, 1100*t*, 1102, 1105*t*, 1108
Progressive systemic sclerosis, 223*t*, 224, 231
Prokinetics, 231
Prolactin, 252, 319, 328, 330–331
Prolactinomas, 330–331, 336
Prolactin-releasing factor, 330
Promethazine, 609–610, 1027, 1036*t*, 1049
Promyelocytic acute myeloid leukemia, 464*f*
Prophylactic cranial irradiation, for brain metastases, 481–482
Propofol, 151, 195, 605*t*, 611, 629, 966, 971–972, 985–989, 986*t*, 1021, 1036*t*
Propofol infusion syndrome, 989
Propranolol, 592, 1049
  during pregnancy, 582
  pregnancy contraindications for, 582, 592
Proptosis, 297, 297*f*, 416*t*, 421, 425, 425*t*, 426*t*, 430–431, 449–450, 456, 483*t*, 700
Propylthiouracil, hyperthermia and, 666*t*
Prosodic abnormalities, as functional disorder, 943
Prostaglandin E_1 (alprostadil), 319, 488, 564, 573–574
Prostaglandin synthetase inhibitors, 142–143
Prosthetic heart valves, 76
Prosthetic valve endocarditis, anticoagulation in, 96
Protein C, 176–177, 177*f*
  deficiency of
    cerebral venous thrombosis and, 471–472
    neurologic manifestations of, 349*t*, 471–472
    venous thrombosis risks, 471–472
  in hemorrhagic disease of newborn, 462
Protein kinase C, 314
Protein S, 176–177
  deficiency of, 471–472
  in hemorrhagic disease of newborn, 462
Prothrombin, deficiency of, 348*t*
Prothrombin G:A 20210 mutation, 177, 472
Prothrombotic systemic inflammatory response, 47–48
Protozoan infections
  African trypanosomiasis, 828–829, 828*f*
  cerebral amebiasis caused by *Entamoeba histolytica*, 831
  cerebral toxoplasmosis
    asymptomatic, 825
    congenital, 825–826
    cranial imaging of, 826*f*, 827
    diagnosis of, 827
    in immunocompromised patients, 827
    magnetic resonance imaging of, 826*f*, 827
    manifestations of, 825
    pyrimethamine and sulfonamide for, 827
    Toxoplasma gondii as cause of, 825
    transmission of, 825
  characteristics of different infections, 822*t*
  malaria
    antimalarial therapy for, 824
    cerebral, 821–825
    diagnosis of, 824
    global distribution of, 821–822, 823*f*
    laboratory tests, 824
    manifestations of, 823
    pathogenesis of, 822–823
    prevalence of, 821–823

Protozoan infections (*Continued*)
    species that cause, 822
    treatment of, 824
  primary amebic meningoencephalitis, 829–831, 830f
Provigil. *See* Modafinil
Proximal diabetic neuropathy. *See* Diabetic lumbosacral plexopathy
Pseudallescheria boydii, 811
Pseudoathetosis, 443, 891
Pseudobulbar palsy, 219, 275, 362t, 456, 524, 633, 1042
Pseudoephedrine, 605, 611, 1026, 1048t
Pseudohypoparathyroidism, 278, 338
Pseudomonas aeruginosa
  bacterial meningitis caused by, 689t, 690
  infections with, 387, 399, 694, 695t
Pseudomyotonia, 290, 519
Pseudoneurotoxic disorders, 648
Pseudopolycythemia, 456–457
Pseudotumor cerebri. *See* Idiopathic intracranial hypertension
Pseudoxanthoma elasticum, 186, 348t
Psilocybin, 643
Psychiatric disorders and headache, 1053–1054
Psychosis
  in adrenal insufficiency, 339
  after sedative drug withdrawal, 641
  antiphospholipid antibodies and, 470
  cocaine and, 637
  corticosteroid-induced, 799
  drug-induced, 608
  in Hashimoto encephalopathy, 300, 1034
  in herpes simplex encephalitis, 749–750
  in human immunodeficiency virus meningitis, 747
  in hyperparathyroidism, 337
  in hyperthyroidism, 298
  in hypocalcemia, 278
  in hypoparathyroidism, 338
  in hypothyroidism, 288
  in limbic encephalitis, 507
  manganese toxicity and, 655
  methamphetamine and, 638–639
  with multiple cerebral microemboli, 93
  nitrous oxide and, 644
  phencyclidine and, 643
  postpartum, 326
  in relapsing polychondritis, 393
  in systemic lupus erythematosus, 356, 887–890, 1015
  with treatment for leprosy, 735
  vitamin B_{12} deficiency, 237
  in Wilson disease, 212, 322
Pudendal nerve, 34, 220t, 224, 542, 543f, 559f, 560–562, 562f, 565, 570
Pudendal nerve terminal motor latency, 552–553
Pudendal neuropathy, 224
Pudendal somatosensory evoked potentials, 552
Pulmonary disease, and headache, 19, 1051
Pulmonary function evaluations, 6–7, 13
Pulmonary pathology, dysfunction related to, 18
Pulmonary sarcoid, 847
Pulmonary transplantation, 796
Pulseless disease, 904. *See also* Takayasu arteritis
Punding, 639
Pupil. *See also* Neuro-ophthalmologic disorders
  afferent defect of, 434
  anatomy of, 433–434
  anisocoria, 132, 428, 434–436
  Argyll Robertson, 434, 706–707
  drugs that affect, 614
  examination of, 433
  light response, 434
  near response, 434
  swinging flashlight test of, 434
  tonic, 436
Pure autonomic failure, 129–130
Purkinje cell antibody 2 (PCA-2), 129
Purkinje cell degeneration, in paraneoplastic cerebellar degeneration, 511, 511f
Purkinje cells, 148
Pyomyositis, 782, 1078
Pyrazinamide, 723–725
Pyrethroid insecticides, 658–659
Pyridostigmine bromide
  for gastrointestinal motiity disorder, 233
  for myasthenia gravis, 430, 973–974
  postural hypotension treated with, 141t, 142t, 144
  for postural orthostatic tachycardia syndrome, 132
Pyridoxine
  deficiency of, 202, 236t, 245–246, 306t, 1060t, 1064t, 1072
    clinical manifestations, 245
    diagnosis, 245–246
    etiology, 245
    treatment, 246
  homocystinuria and, 350
  isoniazid and, 617–618, 723, 1014t, 1021
  toxicity, 619, 997t, 1060t, 1063t, 1072

Q

Q waves, 164
QT prolongation, 163–164, 164f
Quadriplegic myopathy, acute, 623–624
Quantiferon gold serum testing, 720
Quantitative sensory testing, for diabetic polyneuropathy, 307
Quantitative sudomotor axon reflex testing (QSART), 139, 312
Quinine, 598, 614–615, 620, 620t, 824, 973
Quinolone resistance in *M. leprae*, 736

R

Rabies virus
  characteristics of, 743t, 755–756
  clinical presentation of, 756
  encephalitis caused by, 755–756
  management of, 756
  transmission of, 755–756
Radiation myelopathy
  early delayed, 533
  late delayed, 533–534
Radiation plexopathy, 494–495, 534–535
Radiation recall, 525
Radiation therapy, 530–536
  indications for
    epidural spinal cord compression, 488–489
    intramedullary spinal cord metastases, 489
  lumbosacral plexopathy caused by, 1062
  malignancies caused by, 495
  nervous system dysfunction caused by, 530–536, 531t, 535t
  neurologic complications of
    to brain, 531–533
    cavernomas, 535, 536f
    cerebral atrophy, 533
    cranial nerves, 534
    early delayed radiation myelopathy, 533
    encephalopathy, 531

    late delayed, 532–533
    late delayed radiation myelopathy, 533–534
    peripheral nerves, 534–535
    radiation necrosis, 532–533, 532*f*
    radiogenic tumors, 535
    SMART syndrome, 533
    vascular abnormalities, 535–536, 536*t*
  in pregnancy, 582
Radiation-induced vasculopathy, 182
Radiculopathy
  aortic disease as cause of, 32
  description of, 1059–1060
Radiogenic tumors, 535
RAGE, 314
Raloxifene, 326
Ramelteon, 919–920, 919*t*, 930
Ramsay Hunt syndrome, 406
Rapamycin inhibitors, mammalian target of, 797–798
Rapid diagnostic tests (RDTs), 824
Rathke pouch, 328–329
Raynaud phenomenon, 176, 340*t*, 353*t*, 357*t*, 367*t*, 458, 527, 893, 898, 903, 1047
  and migraine, 1047, 1052
Recoverin, 503*t*, 513
Recreational drugs
  bath salts, 639–640
  cocaine. *See* Cocaine
  dextromethorphan, 643–644
  flakka, 640
  gamma hydroxybutyrate, 640–641
  hallucinogens, 643
  infectious complications of injection drug use, 645
  intravenous administration of, 645
  marijuana, 644–645
  MDMA, 640
  methamphetamine, 638–639, 639*f*
  neurologic problems caused by, 637
  nitrous oxide, 644, 644*f*
  N-methyl-D-aspartate antagonists, 643
  opiates, 641–643
  sedative-hypnotics, 641
  seizures and, 1020
  tremor and, 1039–1040, 1039*t*
Recurrent laryngeal nerve anatomy, 31
Recurrent laryngeal nerve palsy, 31, 37, 46, 244, 292, 301, 495, 526, 534, 1071–1072
Recurrent meningitis, inflammatory causes of, 847–850
  IgG4-related disease, 849–850
  malignancy, 850
  neurosarcoidosis, 847–848
  primary central nervous system vasculitis, 848–849
  rheumatoid arthritis, 849
Refsum disease, 362*t*, 363–364, 367*t*, 1065*t*, 1074
Regional anesthesia
  antithrombotics and, 983
  cognitive function and, 968, 982
  myasthenia gravis and, 597–598, 973
  neurologic complications of, 980*t*
  neuromuscular disorders and, 988
  neuropathy and, 983
  perioperative headache, 986
  perioperative stroke and, 974
  surgery for Parkinson's disease and, 966
  warfarin and, 983
Regional wall motion abnormalities, after subarachnoid hemorrhage, 162
Relapsing polychondritis, 36, 392–394, 392*t*, 394*f*, 394*t*, 408
Relaxation therapy
  for insomnia, 918
REM parasomnias, 934–935
REM sleep behavior disorder, 212, 467, 916, 921, 935–936, 1101, 1105*t*, 1109
Remifentanil, 987–988
Renal disease. *See also* Dialysis; Dialysis disequilibrium syndrome; Uremic encephalopathy; Uremic neuropathy
  antiepileptic drugs in patients with, 1008–1009
  and headache, 1051–1052
  nephrotic syndrome, neurologic complications of, 259–260
  neurologic dysfunction and
    autonomic neuropathy, 257
    encephalopathy, 251–255, 1089
    hearing loss, 408
    myoclonus, 252–253, 1008
    myopathy, 258
    optic neuropathy, ischemic, 259
    polyneuropathy, 255–257
    restless legs syndrome, 257–258, 442
    seizures in, 255, 1008–1009
    stroke, 258–259
Renal transplantation, 264–265, 795
Renal tubulopathy, diabetes mellitus, and cerebellar ataxia, 362*t*
Renin, 130, 142, 326, 338
Renin-angiotensin-aldosterone system, 104, 124, 126, 131
Repeatable Battery for the Assessment of Neuropsychologic Status (RBANS), 194
Repolarization abnormalities, cardiac, 164
Reserpine, 594, 608, 612, 667*t*, 1027, 1033, 1039, 1039*t*, 1042
  hypothermia and, 667*t*
Respiratory alkalosis, 668
Respiratory dysfunction
  abnormal patterns of respiration, 8*f*
  apraxia of breathing, 9
  central nervous system lesions, 8
    apneustic breathing, 8
    ataxic breathing, 8, 10, 17
    Cheyne–Stokes breathing, 8, 10, 17
    hyperpnea, 8
  central hypoventilation, 9
  central neurogenic hyperventilation, 9
  in central sleep apnea syndromes, 16–17
  cluster breathing, 10
  in congenital myopathies, 15
  diaphragmatic myoclonus, 10
  hiccup, 10
  in inflammatory myopathies, 15
  involuntary respiratory control, disorders of, 9
    acquired central hypoventilation, 9
    congenital central hypoventilation syndrome, 9
  in limb-girdle syndromes, 15
  myopathies as cause of, 15–16
  in myotonic dystrophy, 15
  from neurologic disorders, 5, 10–16
    brain tumors, 16
    demyelinating disorders, 12
    epilepsy, 16
    movement disorders, 11–12
    neuromuscular disorders, 12–16, 12*t*
    spinal cord lesions, 16
    stroke, 10–11
  neuropathies as cause of, 13–14
  patterns of, 7–10

Respiratory dysfunction (*Continued*)
  posthyperventilation apnea, 9
  related to obstructive sleep apnea (OSA), 18–19
    cognitive dysfunction, 18–19
    epilepsy, 19
    headache, 19
    vascular disorders, 18
  related to pulmonary pathology, 18
    hypercapnia, 18
    hypoxia, 18
  restrictive pattern of, 7
  in sleep hypoventilation syndrome, 17. *See also* Sleep apnea
  sneezing and yawning, 10
  in sudden infant death syndrome, 17
  in upper airway obstruction, 16–17
  voluntary respiratory control, disorders of, 9
Respiratory dysrhythmias, 17
Respiratory effort-related arousal, 925–926
Respiratory insufficiency, 13–16, 18
Respiratory pattern generators (RPGs), 4
Respiratory system, 3–19. *See also* Breathing
Rest tremor, 192, 1038–1039, 1039*t*, 1041–1042, 1102
Restless legs syndrome, 206–207, 931–933
  causes of, 932*t*
  iron-deficiency anemia and, 442
  and movement disorders in pregnancy, 591–592
  pregnancy and, 591–592
  sex steroids and, 323
  treatment of, 931–932, 932*t*
  in uremic neuropathy, 256–258, 261, 1071
  in Wilson disease, 212
Reticular activating system, 1086–1088, 1087*f*, 1092–1093, 1097–1098
Reticular reflex myoclonus, 1038
Retinoids, 528–529, 604, 608, 614
Retinopathy
  anemia and, 442
  cancer-associated, 506*t*, 513
  Cockayne syndrome, 359
  diabetes and, 357*t*, 420*t*
  drug-induced, 614
  helminth infection, 822*t*
  hypertensive, 103, 142
  light-near dissociation and, 434
  malarial, 824
  melanoma-associated, 506*t*, 513
  paraneoplastic, 501*t*, 504*t*, 506*t*, 513
  radiation complication, 534, 534*t*
  sickle cell disease and, 445
  Takayasu disease, 36
  Toxoplasma infection, 822*t*
  vitamin E deficiency, 208, 242
Retrobulbar optic neuropathy, 416–417, 416*t*, 418*f*, 419–420, 871, 903
Retrobulbar/posterior ischemic optic neuropathy, 44–45
Retrochiasmal vision loss, 423–424
Retrograde ejaculation, 563, 570–571
Reverse bobbing, 433
Reverse urea effect, 262
Reverse vaccinology, 855
Reversible cerebral vasoconstriction syndrome (RCVS), 340, 584, 899, 1049
Revesz syndrome, 362*t*
Rewarming, for hypothermia, 670–671
Reynaud phenomenon, 893
Rhabdomyolysis, 985, 998*t*, 1005, 1063
  acute, 622
  causes of, 202, 276, 278, 289, 292, 591, 613, 620–621, 640, 642, 644, 668, 973, 985, 988–989, 1035
  critical illness myopathy versus, 1081–1082
  in critically ill patients, 998*t*, 1005
  diagnosis of, 1083–1084
  in exertional heat stroke, 668
  myoglobinuria secondary to, 1084
Rhabdomyosarcoma, 345, 411–412
Rheumatic heart disease, 66*t*, 69, 76, 591, 795
  stroke and, 76
Rheumatoid arthritis (RA), 77, 178, 351, 364–365, 849, 894–897
  carpal tunnel syndrome in, 896, 1064–1065
  central nervous system manifestations of, 895
  cervical myelopathy caused by atlantoaxial subluxation in, 895
  characteristics of, 894
  diagnostic testing, 849
  and headache, 1052
  myelopathy in, 364–365
  pachymeningitis and, 841, 895
  peripheral nervous system manifestations of, 895–896
  presentation, 849
  prevalence of, 894
  risk factors, 849
  sensory neuropathy in, 896–897
  systemic manifestations of, 894–895
  treatment, 619, 849, 897
  ulnar nerve compression in, 895–896
Rhinocerebral mucormycosis, 264, 804
Rhizopus, 810
Ri antibody, 510, 513, 1031, 1037, 1071
Rickets, 247, 379*t*, 380–381, 383
Rickettsia rickettsii, 687–688
Rifampicin resistance, 735–736
Rifampin, 389, 689–690, 692, 723–725, 735–736, 738, 780, 830
Rifapentine (RPT), 736
Rifaximin, 198–199
Riley–Day syndrome, 128, 378*t*
Risk of Paradoxical Embolism (ROPE) score, 73
Risperidone, 606, 611, 924, 1014*t*, 1021, 1042, 1107
Ritalin. *See* Methylphenidate
Rituximab
  in enteroviral meningoencephalitis, 757
  in hemophilia A, 462
  in hepatitis C, 1067
  in idiopathic immune-mediated neuropathy, 1067
  in inflammatory myopathies, 1080
  intrathecal, 530
  neurologic complications of, 517, 528
  in neurosarcoidosis, 882–883
  in paraneoplastic syndromes, 506*t*, 512, 517
  in progressive multifocal leukoencephalopathy (PML), 757
  in relapsing polychondritis, 394
  in Sjögren Syndrome, 892
  in thrombotic thrombocytopenic purpura, 358, 465
  toxicity, 522*t*
Rivaroxaban, 79, 468, 983
Rivastigmine, 225, 1100–1101
Rizatriptan, 1050
Rocky Mountain spotted fever
  meningococcal meningitis, 351, 685
  neurocutaneous manifestations of, 353*t*
Root lesions, in pregnancy, 594–595
Ropinirole, for restless legs syndrome, 931–932, 932*t*

Ross syndrome, 436
Rostral ventral lateral medulla, 158
Rotigotine, 932*t*, 966
Roux-en-Y gastric bypass, 201–202, 209
rpoB gene, 735
RU486, 323
Rubella
  congenital, 406, 860
  maternal, 590
  postinfectious neurologic complications and, 763*t*
  vaccine for, 860
Rufinamide, 1009*t*, 1010*t*
Ryanodine receptor gene, 624, 973
Rydel–Seiffer tuning fork, 305

S

S100 calcium-binding protein B (S100-B), 153–154, 674–675
Sabin poliovirus vaccine, 863
Sacral neuromodulation, 555
Sagittal sinus thrombosis. *See* Cerebral venous sinus thrombosis (CVST)
Salicylate overdose
  hyperthermia and, 666*t*
Salivary drooling (sialorrhea), 225
Salk poliovirus vaccine, 854*t*, 863
Saphenous nerve injury, 46
  during labor and delivery, 596
Saphenous vein, harvesting of
  for CABG, 46
Sarcoidosis
  cardiac, 81–82
  corticosteroids for, 868, 881
  definition of, 407, 868
  diagnosis of, 867
  differential diagnosis of, 877–879, 878*f*
  epidemiology of, 870–871
  gallium-67 scanning for, 877
  general supportive care for, 883
  granulomatous inflammation of, 869, 869*f*, 1081
  historical description of, 868
  immunosuppressive and immunomodulatory treatments, 882–883
  intraparenchymal lesion caused by, 874, 874*f*
  isolated neurosarcoidosis, 879
  laboratory tests, 868, 877
  mortality in, 868
  muscle pathology in, 870
  neurocutaneous manifestations of, 353*t*, 355, 367*t*
  neurologic manifestations of. *See* Neurosarcoidosis
  ocular examination in, 877
  organ involvement in, 868, 868*t*
  osteoporosis risks, 883
  otoneurologic manifestations of, 407
  pathophysiology of, 869–870, 869*f*, 870*f*
  population differences for, 870–871
  and postural orthostatic tachycardia syndrome (POTS), 131
  prognosis for, 868, 883–884
  pulmonary damage in, 869*f*, 877
  sellar masses and, 329, 330*t*
  spinal cord, 875
  systemic, 877
  treatment of, 879–883, 880*f*
SARS-CoV-2 infection, 760–761
S-100B, 153–154, 995
Scedosporium species, 804*t*, 811
Schilling test, 238
Schimke immuno-osseous dysplasia, 348*t*
Schimmelpenning–Feuerstein–Mims syndrome, 361–362, 361*f*. *See also* Linear sebaceous nevus syndrome
Schistosoma spp., 458*t*, 822*t*, 836
Schistosomiasis, 836–837
Schulman–Upshaw syndrome, 358
Schwannomas, 330, 344–345, 401, 404*f*, 408, 535, 1059, 1063–1064
Sciatic nerve, metastases to, 495
Sciatic nerve injury, 390, 595–596
Sciatica, 375
  catamenial, 327
Scleroderma, 36*t*, 224, 362*t*, 367*t*, 368, 500*t*, 665, 893, 894*t*, 1016, 1077*t*, 1080. *See also* Systemic sclerosis
SCN51, 83–84
SCN1A mutation, 1012
Scott syndrome, 463
Seborrheic dermatitis, 349*t*, 359, 362*t*, 366*t*
See-saw nystagmus, 432
Segmental myoclonus, 1033
Segmental spinal myoclonus, 1037
Seizures, 49, 81
  acute symptomatic in children with congenital heart disease, 60–61
  after anesthesia, 985
  after cardiac surgery, 45
  alcohol withdrawal, 628, 1020
  Alzheimer disease and, 969
  anoxic-ischemic encephalopathy and, 1014–1015
  antibiotics and, 1021
  antidepressants and, 1020–1021
  antipsychotic drugs and, 1021
  associated with systemic cancer, 1018–1019
  autoantibodies associated with, 1015*t*
  bacterial meningitis and, 684
  brain abscess and, 693
  calcineurin inhibitors and, 797
  calcium and magnesium imbalance, 1019–1020
  cardiac disease and, 1012
    use of antiseizure medications in cardiac disease, 1012
  cerebral trauma, seizures, and epilepsy, 1021–1022
  cerebral vasculitis, 1015–1016
  chemotherapeutic agents and, 523*t*
  cocaine and, 638, 1020
  connective tissue diseases, 1015–1016
  contrast media and, 958
  in critically ill patients, 1012–1015
  demyelinating disease and, 1016
  diabetes and GAD65 antibodies, 1016
  drugs that cause, 605–606, 612*t*
  early-onset, 1022
  endocrine disorders and, 1019–1020
  fetus effects of, 579
  generalized, 628, 1008, 1091
  glucose metabolism disorders, 1019
  Hashimoto encephalopathy, 1016
  hepatic disease and, 1010–1011
    antiseizure medications and hepatic injury, 1010–1011
  hepatic encephalopathy and, 1009–1010
  human immunodeficiency virus (HIV) and, 1018
  hypernatremic, 276
  hyperthyroidism and, 299
  hypocalcemic, 1019
  hypoglycemia and, 1019
  hyponatremic, 274

Seizures (*Continued*)
  hypothyroidism and, 287–288
  immunosuppressants and, 1017
  incontinentia pigmenti and, 360–361, 361*f*
  infective endocarditis and, 94–95
  inflammatory bowel disease, 1016
  intrathecal contrast media and, 957–958
  ischemic stroke as cause of, 94
  isoniazid and, 1021
  limbic encephalitis, 1015
  linear sebaceous nevus syndrome and, 361–362, 361*f*
  metabolic disorders and, 1019–1020
  multiple sclerosis and, 1016
  neurocutaneous syndromes and, 359–362
  neurocysticercosis and, 832
  new-onset, 57
  nonconvulsive, 1012
  perioperative, 970–971, 985–986, 986*t*
  porphyrias and, 1016–1017
  postcraniotomy, 986
  postoperative, 971
  in post-transplantation period, 787
  posttraumatic, 1021–1022
  in pregnancy, 578–579
  recreational drugs and, 1020
  renal failure and, 253, 1008–1009
  sarcoidosis and, 875, 882
  sedative-hypnotic withdrawal as cause of, 641
  sexual symptoms and, 566
  sodium homeostasis disorders, 1019
  status epilepticus, 1012
  Sturge-Weber syndrome and, 359–360, 360*f*
  systemic lupus erythematosus and, 888
  thyroid disease and, 1016, 1019
  in transplant recipients, 787, 1017–1018
  traumatic brain injury and, 1021
  treatment of, 1013–1014
  viral encephalitis and, 759
Selective serotonin reuptake inhibitors (SSRIs)
  adverse effects, sexual, 571–572, 575
  for cataplexy, 923
  confusional state caused by abrupt cessation of, 608
  and HAND, 769–770
  headache and, 604, 1048
  and movement disorders, 1026, 1027*t*, 1036*t*, 1038, 1039*t*, 1042
  for parasomnias, 934*t*
  and postural orthostatic tachycardia syndrome, 131–132
  premenstrual symptoms and, 326
  and restless legs syndrome, 932*t*
  and seizures, 1020
  serotonin syndrome caused by, 608, 640, 664, 666*t*
Selumetinib, 522*t*, 528, 621*t*, 625
Semantic dementia, 1101–1102
Semmes–Weinstein monofilament test, 305
Sensorineural hearing loss
  aging and, 412
  Alpert syndrome, 270
  in bacterial meningitis, 351, 400, 692
  Cockayne syndrome and, 359
  in connective tissue diseases, 407–408
  description of, 392–393
  eighth nerve lesions, 401
  environmental factors, 411
  hypocalcemia and, 338
  inflammatory bowel disease and, 204, 205*t*, 206
  Lyme disease and, 406
  noise exposure and, 411
  in Ramsay-Hunt syndrome, 406
  in relapsing polychondritis, 392
  syphilis and, 355, 406
  systemic lupus erythematosus and, 408
Sensory neuronopathy. *See also individual diseases*
  acute, 1060
  causes, 1060–1061, 1060*t*
  hereditary, 1060–1061
  human immunodeficiency virus infection, 781–782, 1060
  infectious causes of, 1060, 1060*t*
  paraneoplastic, 503*t*, 506*t*, 508, 510, 515–517, 516*f*, 527, 1060, 1072
  platinum compounds and, 617
  pyridoxine and, 1072
  in Sjögren syndrome, 353*t*, 891–893
  subacute, 515–516, 516*f*
  toxins and, 1061
Sensory neuropathy. *See* Neuropathy; *individual disorders*
Sensory paralytic bladder, 546
Sensory presbycusis, 412–413
Sensory symptoms, functional, 942*t*, 943
Sepsis
  cerebral ischemia in, 995
  mechanisms of, 993–994
  metabolic encephalopathy and, 1090
  organs affected by, 994
SEPT9 gene, 595
Septic emboli
  cerebral abscess and, 97–98, 804
  in children with congenital heart disease, 58–60
  meningitis and, 97, 804
  stroke and, 88, 348*t*, 350, 645
  to vertebrae, 387
Sepsis-associated encephalopathy, 993–996
  clinical presentation of, 995
  definition of, 993
  electroencephalographic findings, 995, 996*f*
  epidemiology of, 993
  evaluation of, 995
  magnetic resonance imaging of, 995
  pathogenesis of, 994–995
  sepsis mechanisms, 993–994
Septic intracranial thrombophlebitis, 683, 699–700
Serotonin and norepinephrine reuptake inhibitors
  neuropathic pain treated with, 315, 892
  side effects of, 315, 604
Serotonin syndrome, 608, 613, 640, 643–644, 662*t*, 664, 666*t*, 668, 967, 985, 1034–1035, 1039
Sevoflurane, 971, 988
Sex hormones. *See also* Pregnancy
  description of, 317–318
  neurological disorders and
    Alzheimer disease, 324–325
    chorea, 321–322
    depression, 326
    epilepsy, 320–321
    gliomas, 323
    intracranial hypertension, 327
    meningiomas, 323
    migraine, 318–319
    movement disorders, 321–323
    multiple sclerosis, 324
    nervous system neoplasms, 323–324
    neuromuscular diseases, 327

        neuropsychiatric disorders, 325–326
        parkinsonism, 322
        porphyrias, 325–326
        premenstrual syndrome, 326
        psychosis, 326
        sleep disorders, 326–327
        stroke, 319–320
        Wilson disease, 322–323
    organizational effects of, 317–318
    during sleep, 6
Sexsomnia, 935
Sexual dysfunction. *See also* Erectile dysfunction
    amyotrophic lateral sclerosis and, 571
    aortic disease as cause of, 34–35, 35*t*
    brain injuries and, 565
    cauda equina lesions and, 569–570
    cerebrovascular disease and, 565–566
    description of, 557–558
    diabetes mellitus and, 311–312
    diabetic polyneuropathy and, 570–571
    drugs that cause, 604
    epilepsy and, 566
    evaluation of
        clinical examination, 563
        genital reaction and arousal, 563–564
        history, 563
        hormone measurement, 565
        investigations of, 563–565
        neurologic function, 564–565
    extrapyramidal disorders and, 567
    head injuries and, 565
    hypothalamic and pituitary disorders and, 567–568
    localized nerve lesions and, 570
    lumbar stenosis and, 570
    multiple sclerosis and, 568
    multiple system atrophy and, 567
    Parkinson disease and, 566–567
    polyneuropathies and, 571
    renal failure, chronic, and, 571
    sacral lesions, 564, 572*t*
    spinal cord lesions and, 568–569
    spinal malformations and, 570
    suprasegmental lesions, 564, 564*t*
Sexual function
    aging-related changes in, 562–563
    arousal, 558–560
    desire, 558
    excitement, 558–560
    lesions that affect. *See* Sexual dysfunction
    orgasm, 560–561, 561*f*
Shaken baby syndrome, 357*t*
Shapiro syndrome, 663–664
Sheehan syndrome, 333
Shift work disorder, 914, 922*t*, 929–930
Shiga toxin, 466
Shingles. *See* Cutaneous zoster
Shingrix vaccine, 857
Shivering, 661, 663–665, 669–670
Short QT interval syndrome, 83
Shulman syndrome, 457
Shy–Drager syndrome. *See* Multiple system atrophy (MSA)
SIADH. *See* Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Sialorrhea, 225, 1121
Sicca syndrome, 365, 893–894
Sick sinus syndrome. *See* Chronic sinoatrial disorder
Sickle cell anemia/disease, 178, 444–445
    neurologic manifestations of, 245, 335*t*, 416*t*, 444–445
    stroke in, 178, 186, 444, 583–584
    transcranial Doppler ultrasonography in, 178
Sideroblastic anemia, 240, 245, 447
Sigmoid sinus thrombosis. *See* Cerebral venous sinus thrombosis (CVST)
Sildenafil (Viagra), 257, 311, 572–573, 575, 614–615, 1048*t*
Silicone biomaterial (PTQ), for fecal incontinence, 225
Single ventricle heart disease, 56
Sinoatrial disorder, chronic, 72–73
Sirolimus, 797–798
Situation-related seizures, 1007–1008
Sjögren syndrome, 365, 890–893, 1016
    autonomic neuropathy in, 892
    central nervous system disease, 891
    definition of, 890
    diagnosis of, 890–891
    distal sensory neuropathy in, 892
    hearing loss in, 408
    mononeuritis multiplex in, 896–897
    neurocutaneous manifestations of, 353*t*, 365
    pathogenesis of, 890–891
    peripheral nervous system disease, 891–892
    seizures in, 1016
    sensory neuronopathy in, 353*t*, 891–892
    systemic disease, 890–891
    treatment, 892–893
    trigeminal neuralgia in, 892
    trigeminal neuropathy in, 891
Skew deviation, 424–427, 425*t*, 429, 980, 1093
Skull-base metastases
    clinical features of, 482
    cranial neuropathy and, 482, 483*t*
    diagnostic studies of, 482, 484*f*
    differential diagnosis of, 483
    epidemiology of, 482
    magnetic resonance imaging of, 484*f*
    pathophysiology of, 482
    prognosis for, 483
    treatment of, 483
Skull-base syndromes, 483*t*
SLC30A10 gene, 456
Sleep. *See also* Sleep disorders
    age-related requirements, 914
    ascending arousal system and, 914
    breathing disorders associated with. *See* Breathing, disordered, with sleep
    coma versus, 1088
    definition of, 912
    dopamine and, 914
    electroencephalography of, 912, 913*f*, 1088
    estrogen effects on, 326–327
    latency to onset of, 916
    lifespan patterns of, 913–914
    neuroanatomy of, 914–915
    in newborns, 913
    non-rapid eye movement (NREM)
        description of, 912
        monoaminergic system in, 914
    nonrestorative, 917
    onset of, 914
    physiology of, 912–914, 913*f*
    rapid eye movement (REM)
        characteristics of, 912–913, 913*f*
        cholinergic neurons in, 914–915

Sleep (*Continued*)
        percentage of time in, 914
    stage N1, 912, 913*f*
    stage N2, 912, 913*f*
    stage N3, 912, 913*f*
    stage wake of, 912
Sleep apnea, 6, 16–17
    age and, 924
    atrial fibrillation and, 925, 937
    central. *See* Central sleep apnea (CSA) syndromes
    cognitive decline secondary to, 937
    genetic predisposition, 925
    health risks associated with, 937
    obesity and, 924
    obstructive. *See* Obstructive sleep apnea (OSA)
    refractory hypertension and, 925
    risk factors for, 924
    stroke risks, 925, 937
Sleep deprivation, 1052
Sleep diary, 915
Sleep disorders, 212
    actigraphy of, 916
    in Alzheimer disease, 936
    approach to, 915–916
    circadian rhythm. *See* Circadian rhythm disorders
    clinical evaluation of, 915
    dementia and, 1109
    description of, 912
    electroencephalography of, 915
    electromyography of, 915
    in epilepsy, 936
    excessive daytime sleepiness and, 912, 921
    and headache, 937
    and headache disorders, 1048
    home sleep study for, 916
    hypersomnias. *See* Hypersomnias
    insomnia. *See* Insomnia
    laboratory tests, 915–916
    maintenance of wakefulness test for, 916
    morbidity and mortality of, 915
    multiple sleep latency test for, 916
    parasomnias. *See* Parasomnias
    in Parkinson disease, 936
    physical examination, 915
    polysomnography of, 915–916
    REM sleep behavior disorder, 921, 934*t*, 935, 1101, 1105, 1109
    in stroke, 937
Sleep hygiene, 677*t*, 918*t*, 923, 1109
Sleep hypoventilation syndrome
    neurologic causes of, 17*t*
    respiratory dysfunction associated with, 17
Sleep paralysis, 921
Sleep questionnaire, 915
Sleep switch, 915
Sleep terrors, 933–934
Sleeping sickness, 828. *See also* African trypanosomiasis
Sleep-related breathing disorders, 924–927. *See also* Sleep apnea; Sleep hypoventilation syndrome
    epidemiology of, 924
    obstructive sleep apnea. *See* Obstructive sleep apnea (OSA)
    upper airway stimulation of, 927
Sleep-related eating disorders, 934*t*, 935
Sleep-related movement disorders, 931–933
    definition of, 931
    periodic limb movements, 933
    restless legs syndrome. *See* Restless legs syndrome
Sleep-wake cycle, 914
Sleepwalking, 933
Slow-delayed potassium channels, 158
Small bowel and multivisceral transplantation, 796–797
Small molecule inhibitors, 528
Smallpox vaccine, 857–858
SMART syndrome, 533
Smell disorders, drug-induced, 615
Sneddon syndrome, 67, 351, 470
    and stroke, 176
Sneezing, 10, 224, 375, 384, 970
Sodium, 273–277, 1019. *See also* Hypernatremia; Hyponatremia
Sodium oxybate, 922*t*, 923
Solid organ transplantation (SOT), 793–797
    cardiac transplantation, 795–796
    hepatic transplantation, 793–795
    pancreatic transplantation, 796
    pulmonary transplantation, 796
    renal transplantation, 795
    small bowel and multivisceral transplantation, 796–797
Solriamfetol, 922–923
Solvents, organic, 651–652, 1042
Somatosensory evoked potential (SSEP), 149, 151–152, 238, 1094
    cardiac arrest prognostication using, 151–152, 152*f*
    for neurosarcoidosis, 878
    spinal cord function evaluations using, during surgery, 40
Somnambulism. *See* Sleepwalking
Sparganosis, 833–834
Spastic paraplegia, cutaneous manifestations of, 366*t*
Speech and voice disorders, functional, 942*t*, 943
Sphincter electromyography, 551–552
Spinal anesthesia
    abducens nerve palsy after, 985
    and amyotrophic lateral sclerosis, 972
    cauda equina syndrome secondary to, 984
    hearing loss after, 956, 984–985
    intracranial hypotension after, 970
    in multiple sclerosis, 967, 988
    multiple system atrophy and, 988
    myoclonus from, 1036*t*
    pupillary changes caused by, 985
    radiculopathy from, 1059
    transient neurologic symptoms after, 984
Spinal angiography, 960–961
Spinal arteriovenous malformation, 377, 548*t*, 587–588
Spinal cord
    circulation of, 22–24, 23*f*, 25*f*
    compression of, 38*t*, 39, 362*t*, 364–365, 374, 387, 389–391, 445, 449, 453–454, 456–457, 485–486, 533–534, 645, 723, 763, 783, 799, 822*t*, 895, 957
    disease of, in HIV-infected patients, 781
    drug-induced disorders of, 616
    hemorrhage in, after radiation therapy, 535–536
    lymphoma involvement of, 453
    metastases of
        classification of, by anatomic location, 485, 486*t*
        epidemiology of, 485
        epidural spinal cord compression, 485–489
        intramedullary, 489, 490*f*
    paraneoplastic syndromes of, 514–515
    primary (CNS) lymphoma of, 454
    puncture of, 957
    sarcoidosis of, 875
    subacute combined degeneration of, 210, 236, 240, 444, 616
    trauma of. *See* Spinal cord injury
Spinal cord dysfunction after bariatric surgery, 202

Spinal cord injury
  ankylosing spondylitis and, 390–391
  autonomic consequences of, 127–129
  bladder disturbances, 545–546
  bowel problems in, 227
  cervical, 16
  ejaculation affected by, 569
  fecal incontinence after, 227
  gut dysmotility and, 228
  ileus after, 227
  incomplete, 569
  ischemia. *See* Spinal cord ischemia
  multiple sclerosis and, 228
  neuromyelitis optica and, 228
  postural hypotension caused by, 127–129
  sexual dysfunction in, 568
  stroke. *See* Spinal cord ischemia
Spinal cord ischemia, 22–28
  anatomy of circulation, 22–24, 25*f*
  anterior spinal artery, 22–23
  aortic disease as cause of, 24–28, 37–38
  aortic surgery as cause of, 25–26, 26*f*, 26*t*, 39–40, 40*t*
  epidural hematoma and, 982–983
  intermittent, claudication and, 28
  intraoperative adjuncts to avoid, 40
  in patients on ECMO, 49
  polycythemia and, 456
  posterior spinal artery, 23–24
  in pregnancy, 25
  after renal transplantation, 795
  during surgery and procedures on aorta, 40*t*
  syndromes, 24–28
    anterior spinal artery syndrome, 27
    description of, 24–25
    intermittent claudication, 28
    motor neuron disease, 27, 27*f*
    posterior spinal artery syndrome, 27–28
    unilateral cord syndromes, 28
Spinal muscular atrophy (SMA), 12*t*, 13, 363
Spinal myoclonus, 1037–1038
Spinal shock, 127, 546, 568
Spinal stereotactic radiosurgery, 488–489
Spine
  degenerative disease of
    cervical disc disease/spondylosis, 373–375, 374*f*, 545, 957, 1058–1059
    lumbar disc disease, 375–376, 376*f*
  epidural abscess of, 697–699
  malformations of, 570
  Paget disease involvement of, 385
  stenosis of, 376–377, 390–391
  tuberculous arachnoiditis of, 722–723
  tumors of, 485–489, 487*t*, 490*f*
Spinobulbar reflex, 545
Spinocerebellar ataxia, 362*t*, 405, 932
Spirochetal infections, 703–715. *See also* Lyme disease; Syphilis
Spirometra spp., 833
Spondylolisthesis, 373, 377
Spondylosis, 373–375, 545, 957, 1058–1059
Sporothrix schenckii, 804*t*, 809, 814
Sporotrichosis, 809
SQSTM1 mutations, 384
St. Louis encephalitis virus, 687, 741–742, 743*t*, 746, 755, 1040
Stac3 protein, 664
Staphylococci, 76–77, 91–92
Staphylococcus aureus
  bacterial meningitis, postoperative, caused by, 684
  brain abscess and, 695*t*
  infective endocarditis risks, 88–92, 96–98
  myoglobinuria caused by, 1083*t*
  osteomyelitis caused by, 387
  otitic meningitis, 399
  pyomyositis associated with, 782, 1078
Statins, 621
  anti-inflammatory effect of, in HAND, 769–770
  for cerebrotendinous xanthomatosis, 363
  cognitive impairment and, 609
  cramps and, 624
  during pregnancy and lactation, 584–585
  insomnia and, 917*t*
  intracranial atherosclerosis and, 117
  and ischemic stroke risk, 172
  myasthenia gravis and, 620
  myopathy caused by, 620–622, 620*t*, 622*f*, 1077*t*, 1083
  peripheral neuropathy and, 618–619
  and postoperative stroke, 50
  prevention of complications and, 975
Status epilepticus, 60–61, 628
  alcohol withdrawal, 628, 1020
  anoxic-ischemic, 1014–1015
  cardiac disease/surgery and, 152, 1012
  convulsive, 1008, 1019
  in critical illness, 1012
  delayed recovery from anesthesia and, 979–981
  and DIC, 464
  drugs that induce, 605–606, 1021
  fosphenytoin for, 1012
  in Hashimoto encephalopathy, 300
  and hyperthermia, 662
  in hyperthyroidism, 298
  hypoglycemic, 304, 1019
  in hypothyroidism, 288
  ketamine for, 989
  in multiple sclerosis, 1016
  myoclonus, 149–151, 1014–1015, 1033
  myoglobinuria and, 1083*t*
  neurogenic pulmonary edema and, 10
  nonconvulsive, 253, 526, 981, 995, 1012, 1093–1094
  in porphyria, 1017
  in postinfectious encephalomyelitis, 761
  in pregnancy, 578
  propofol infusion syndrome and, 989
  refractory, 989
  in renal failure, 253, 255, 1008
  treatment of, 971, 989, 1021
Steal syndrome, 30–31, 30*f*, 261–262, 384, 1063
Stellate ganglion, 158, 493–494
Stenting, 51, 117–118, 168, 182, 378, 405, 535, 904, 961–962
Stereotactic body radiotherapy (SBRT), 488–489
Stereotactic radiosurgery
  for brain metastases, 480–481
  for epidural spinal cord compression, 488–489
  for skull base metastases, 483
Stevens–Johnson syndrome, 751*t*, 1011
Stiff skin syndrome, 366*t*
Stiff-person syndrome, 501*t*, 506*t*, 515
Stiripentol, 1009*t*
Stokes–Adams attacks, 83, 113
Streptococci, 91–92, 684
Streptococcus pneumoniae, 97, 179*t*, 399, 683, 788, 854*t*, 1083*t*
  bacterial meningitis caused by, 684–685, 692
  otitic meningitis, 399–400

Streptokinase, 619
Streptomycin, 208, 410, 613–615, 617*t*, 618, 723
Stridor, 11, 16
  definition of, 16
  in multiple system atrophy, 11, 1105*t*, 1109
  neurologic causes of, 16, 279
Stroke. *See also* Cerebral ischemia; Hemorrhage; Ischemic stroke
  after coronary artery bypass grafting, 44–45
  after transcatheter aortic valve replacement, 50
  alcohol and, 635
  antiphospholipid antibodies in, 470–471
  aortic disease as cause of, 28–31, 118
  aspirin prophylaxis, 114, 116–117, 975
  atherosclerosis as cause of, 29, 29*t*, 117–118
  blood lipids and, 172
  brain imaging and, 44
  cardioembolic, 58, 65–76, 173
    atrial fibrillation leading to, 69, 173
    brain and vascular imaging, 67–68
    clinical features, 67
    in the context of myocardial infarction, 74
    echocardiography, 68–69
    electrocardiographic monitoring, 69
    patent foramen ovale (PFO), 173
  carotid artery stenosis and, 115–117, 116*t*
  cerebral angiography and, 959–960
  in children with congenital heart disease, 55*f*, 56–57
    neuroimaging for, 58
  clopidogrel and, 113–114, 118, 957, 975, 983
  diabetes mellitus and, 172
  drugs that cause, 183, 604–605
    alcohol, 184, 184*f*
    amphetamines, 184–185
    anabolic androgenic steroids, 183–184
    antihypertensive drugs, 605
    cannabis and cannabinoids, 185
    cocaine, 185
    estrogens, 183
    migraine medications, 185
    oral contraceptives, 604–605
    tamoxifen, 605
    tobacco, 184
  dysphagia and, 219–221
  elective surgery after, 976
  endocarditis and, 76–77, 92–96, 645
  erectile dysfunction after, 565–566
  Fabry disease and, 186, 267, 347–349
  genetics of, 185–186
  gut dysmotility and, 225
  hematologic disorders, 175–178
    antiphospholipid antibody syndrome, 175–176
    cryoglobulinemia, 178
    factor deficiencies, 176–177
    inherited thrombophilias, 177–178
    sickle cell anemia, 177–178
    Sneddon syndrome, 176
  hemorrhagic. *See* Hemorrhagic stroke; Intracerebral hemorrhage (ICH); Intracranial hemorrhage
  in HIV-infected patients, 773–774
  homocysteine and, 172–173
  hormone replacement therapy and, 320
  hypertension and, 101, 103–105, 114, 172
  hyperthyroidism and, 299
  incidence of, 105*f*
  infections, 178–180
  intracranial hemorrhage. *See* Hemorrhage; Intracerebral hemorrhage (ICH); Intracranial hemorrhage
  ischemic. *See* Ischemic stroke
  kidney disease and, 259–260
  lacunar, 111–114
  mechanical ventilation after, 11
  migraine, stroke prevention in, 183
  movement disorders caused by, 1024, 1033, 1038
  neurocutaneous disorders and, 347–351
  oncology and, 181
    cancer therapy, stroke related to, 182
    coagulation disorders in cancer patients, 181
    direct tumor effects, 182
    intracerebral hemorrhage, 182
    nonbacterial thrombotic endocarditis (NBTE), 181–182
  oral contraceptives and, 183, 319
  perioperative, 44, 50–51, 974–976
  postmenopausal hormone replacement therapy, 320, 604–605
  in pregnancy, 583–586
  prevention of, 78–81, 114
    acute myocardial infarction, 80
    anticoagulant therapy for atrial fibrillation, 78–79, 114
    cardiomyopathy and left ventricular dysfunction, 80
    patent foramen ovale, 80–81
    treatment decisions, 79–80
  recurrence in children with CHD, 57
  respiratory dysfunction secondary to, 10–11
  risk factors for, 70–71, 103–105
  sex hormones and, 319–320
  sex-specific risk factors of, 174, 175*t*
  sleep apnea and, 925, 937
  subarachnoid hemorrhage. *See* Subarachnoid hemorrhage
  subclavian (cerebral) steal, 29–31
  systemic lupus erythematosus and, 180–181, 888
  temporal arteritis and, 903
  testosterone replacement therapy and, 604–605
  transient emboligenic aortoarteritis and, 29
  tremor and, 1038
  urinary incontinence after, 544
  warfarin efficacy for stroke prevention in atrial fibrillation, 78*t*
  women's health and, 173–175
    menopause, 175
    stroke in pregnancy, 174–175, 583–586
Strongyloides stercoralis, 834, 834*f*
Strongyloidiasis, 458*t*, 834, 834*f*
Sturge–Weber syndrome, 359–360, 360*f*
Subacute combined degeneration, 210, 236, 240, 444, 616
Subacute myelo-opticoneuropathy (SMON) syndrome, 615
Subacute necrotizing myelopathy, 514
Subacute sclerosing panencephalitis, 847, 1037, 1043
Subarachnoid hemorrhage, 105, 107–108, 110–111, 158, 162, 167–168, 274–276, 688
  alcohol and, 184, 635
  bacterial meningitis versus, 688
  B-type natriuretic peptide levels after, 163
  cardiac function after, 162
  cardiac manifestations of, 157–158, 162, 165
  cardiac myocytolysis, 157–158
  cardiac rhythm disturbances after, 163*f*, 164*f*, 165, 167
  cerebral aneurysm rupture as cause of, 105, 107–108, 108*f*, 270, 1093
  cerebral vasospasm after, 66, 107–108, 167–168, 274–275, 639
  clinical presentation of, 107
  coarctation of the aorta and, 38

  - cocaine and, 185
  - coronary plaque rupture and, 168
  - diastolic dysfunction after, 162
  - drugs that cause, 604–605
  - environmental risk factors for, 105
  - genetic factors, 105
  - in hemorrhagic disease of the newborn, 462
  - in hereditary hemorrhagic telangiectasia, 349
  - hormone replacement therapy and, 320
  - hypertension and, 172, 1049
  - hyponatremia and, 274–276
  - imaging for, 1093
  - infective endocarditis and, 76–77, 92–94, 645
  - intracranial vascular anomalies as cause of, in pregnancy, 586*f*, 587
  - left ventricular dysfunction after, 162
  - methamphetamine and, 639
  - mycotic aneurysm rupture as cause of, 77, 91, 91*f*, 93–94, 645
  - oral contraceptives and, 319–320, 605
  - outcome of, 107*t*
  - in paroxysmal nocturnal hemoglobinuria, 445
  - in pregnancy, 174, 583, 586–587, 586*f*
  - prognosis for, 107
  - with recreational drug use, 605, 639
  - recurrent, 107–108
  - regional wall motion abnormalities in, 162
  - risk factors for, 105–106
  - during sexual activity, 575
  - in sickle cell disease, 444
  - signs and symptoms of, 587
  - stroke caused by, 107
  - T waves in, 164
  - troponin I levels in, 162–163, 167
- Subclavian steal syndrome, 29–31, 30*f*
  - coronary, 30–31
  - neurologic complications of, 30
- Subdural empyema
  - antibiotics for, 697
  - clinical presentation of, 696–697
  - definition of, 695–696
  - diagnosis of, 697
  - etiology of, 696
  - magnetic resonance imaging of, 697
  - neurologic deficits in, 696–697
  - paranasal sinusitis and, 696
  - treatment of, 697
- Subdural hematoma
  - coma and, 1086–1088, 1088*t*
  - dementia and, 1100*t*, 1103–1104
  - description of, 449
  - dialysis and, 260
  - empyema and, 696
  - headache and, 575
  - hematologic malignancy and, 448–449
  - hemophilia A and, 462
  - hypernatremia and, 276
  - after lumbar puncture, 1050
  - metastases and, 484
  - myelography and, 957
  - parkinsonism and, 1042, 1045
  - polycythemia and, 456
  - shaken baby syndrome and, 357*t*
- Subendocardial hemorrhage, after stroke, 159–160
- Substance abuse, and headache, 1054
- Subunit vaccines, 854–855
- Succinylcholine, 1002
  - amyotrophic lateral sclerosis and, 988
  - in demented patients, 969
  - malignant hyperthermia and, 664, 967, 972, 985, 988
  - in motor neuron disease, 972
  - myalgia and, 624
  - in myasthenia gravis, 973, 1002
  - myoglobulinemia and, 1083*t*
  - in neuromuscular disorders, 972
  - neuromuscular junction disorders and, 1075*t*
  - Parkinson disease and, 987
- Sudden infant death syndrome, 17
- Sudden unexplained death in epilepsy (SUDEP), 165–166, 1012
- Sudden unexplained nocturnal death syndrome (SUNDS), 83–84
- Sudomotor function, 139–140. *See also* Sweat tests
- Sudomotor neuropathy, 312
- Sulfonamides, 620
- Sumatriptan, 581–582, 1050
  - during pregnancy and lactation, 581–582
  - menstrual migraine treated with, 319
- Sundowning, 936, 1106–1107, 1109
- Superior oblique myokymia, 433
- Superior sagittal sinus, 206, 699–700, 699*f*, 1093
- Superior semicircular canal dehiscence syndrome, 401–402, 404*f*
- Suprachiasmatic nucleus, 920, 931, 936, 1087*f*, 1107
- Supraventricular tachycardias, 71, 83, 164–165, 168
- Sural nerve biopsy, 204, 295, 307, 515, 652
- Suramin, 522*t*, 617*t*, 618, 829
- Suvorexant, 919*t*, 920
- Sweat tests, 139–140, 139*f*, 140*f*, 232, 312
- Swine flu, 862, 1069
- Sydenham chorea, 321–322, 509, 591, 1024, 1028, 1032, 1044
- Sympathetic skin response, 140, 312, 564*t*, 565, 732
- Sympathomimetic drugs, 144. *See also individual drugs*
- Syncope, 81–84, 132–133. *See also* Postural hypotension
  - aortic coarctation and, 39
  - cardiac, 133
  - cardiac causes of, 81–84
    - arrhythmias
      - channelopathies, 83–84
      - conduction abnormalities, 83
    - structural heart disease, 81–83
  - carotid sinus, 133
  - clinical features to differentiate generalized seizures from, 82*t*
  - clinical manifestations, 81, 132
  - definition of, 132
  - deglutition, 133
  - in elderly, 80, 126
  - exertional, 133
  - features associated with cardiac and noncardiac causes of, 82*t*
  - heat stroke and, 668
  - hyperventilation and, 133
  - micturition, 133
  - neurally mediated, 133
  - patient management, 140–145
  - postural hypotension as cause of, 126, 132, 616
  - Riley–Day syndrome, 128
  - sick sinus syndrome, 72
  - subclavian steal and, 30
  - Valsalva maneuver as cause of, 133
  - vasovagal, 133, 144, 956
  - in ventricular arrhythmia, 81–83
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
  - causes of, 335–336, 336*t*, 527, 754

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) (*Continued*)
  diagnosis of, 335–336
  hyponatremia and, 274–275, 526
  as paraneoplastic syndrome, 500*t*
  treatment of, 275, 759
Synthetic cannabinoids, 185, 606
Synucleinopathies, 547, 935, 1100*t*, 1101, 1104–1105, 1108–1109
Syphilis
  aortitis, 36–37
  background of, 704
  benzathine penicillin for, 707
  central nervous system manifestations of, 1091
  cerebrospinal fluid examination for, 705
  chancres caused by, 706
  clinical features of, 706–707, 845–846
  congenital, 590, 707
  cutaneous lesions and, 353*t*, 354–355, 354*f*
  dementia and, 707, 1103
  diagnosis of, 704–706, 846, 1103
  general paresis of insane (GPI), 707, 1103
  human immunodeficiency virus infection and, 707
  latent, 707
  maternal, in pregnancy, 590
  meningovascular, 706, 845–846
  neurologic manifestations of, 706, 1103
    HIV and, 707, 845
  otosyphilis, 406
  pupillary responses, 434
  serologic testing for, 705
  and stroke, 180, 845–846, 1091
  symptomatic nervous system involvement in, 706
  tabes dorsalis, 180, 353*t*, 546, 706–707, 845–846
  treatment of, 707, 846
Syringomyelia, 127, 546, 956
Systemic inflammatory response syndrome (SIRS), 14, 197, 994
  description of, 197, 199, 994
  encephalopathy associated with, 994
Systemic lupus erythematosus (SLE), 77, 175, 356–358, 459, 885–890, 888*t*, 1047, 1052, 1090
  anticardiolipin antibodies in, 887
  antiphospholipid antibodies in, 887–888, 1015, 1030
  antiphospholipid syndrome and, 887, 890, 1016, 1030, 1045
  aseptic meningitis in, 888–889
  carpal tunnel syndrome in, 889
  cerebral vasculitis in, 1052
  cerebrovascular disease in, 888
  chorea in, 322, 591, 887–889, 1030
  cognitive dysfunction in, 888
  cranial neuropathy in, 888*t*
  cutaneous lesions in, 349*t*, 350–351, 356–357, 367*t*, 886*t*
  diagnostic criteria for, 886
  encephalopathy in, 1090
  headaches in, 888
  hemorrhagic stroke in, 888
  ischemic stroke in, 887–888
  migraine headaches in, 888, 1047, 1052
  myasthenia gravis and, 1076
  neurocutaneous manifestations of, 349*t*, 356–357, 362*t*
  neuropsychiatric manifestations of, 470, 1015–1016, 1091
  neuropsychiatric systemic lupus erythematosus (NPSLE), 887–889
  nonbacterial endocarditis and, 77, 181–182, 887
  and parkinsonism, 1044
  peripheral nervous system disease, 889, 1063*t*, 1066*t*
  polymyositis in, 897
  polyneuropathy in, 889
  and posterior reversible encephalopathy syndrome (PRES), 888
  psychosis in, 888–890
  seizures in, 888, 1015
  sensorineural hearing loss caused by, 408
  stroke in, 180–181, 887–889
  systemic disease, 885–887
  treatment, 889–890
  thrombosis risks in, 469
Systemic sclerosis, 368, 893–894. *See also* Scleroderma
  central nervous system disease, 893
  peripheral nervous system disease, 893
  systemic disease, 893
  treatment, 894
Systemic vasculitis, 368–369, 900–902
  central nervous system disease, 902
  peripheral nervous system disease, 902
  systemic disease, 900–901
  treatment, 902

T

Tabes dorsalis, 128, 180, 353*t*, 546, 706–707, 845–846
Tacrolimus, 797, 898
  neurologic complications of, 121, 267, 522*t*, 523*t*, 606, 611, 612*t*, 617*t*, 619, 621*t*, 786, 797, 798*t*, 888, 898, 1017, 1039*t*, 1064*t*
  for paraneoplastic syndromes, 506, 512
  for polymyositis, 1080
Tadalafil (Cialis), 311, 573, 614–615
Taenia solium, 822*t*, 831–832, 846, 1029*t*, 1079
Takayasu arteritis (TAK), 36, 351, 904
  aortic involvement, 29, 36, 904
  aortic valve insufficiency in, 904
  central nervous system manifestations of, 904
  coarctation of the aorta associated with, 38
  epidemiology of, 36
  neurocutaneous manifestations of, 349*t*, 351
  signs and symptoms of, 36, 351, 904
  syphilitic aortitis versus, 36
  systemic disease, 904
  treatment of, 904
Takotsubo cardiomyopathy, 161–162
Tamoxifen, 323, 326, 522*t*, 523*t*, 605, 614, 1039*t*, 1048*t*
Tangier disease, 1063*t*, 1074
Tapentadol, 987, 1052
TAR DNA-binding protein of 43kDa (TDP-43), 386, 1100*t*, 1101–1102
Tardive dyskinesia, 12, 323, 609–610, 1027, 1033
  drugs that cause, 609–610, 1027
Tardive dystonia, 610, 1027–1028, 1033
Tardive myoclonus, 1035
Tardive syndromes, 1027
Targeted temperature management, 148, 150–152
Tasimelteon, 931
Taste disorders, drug-induced, 615
Tauopathies, 1100*t*, 1101–1103
  chronic traumatic encephalopathy, 679, 1102–1103
  corticobasal degeneration, 1102, 1105*t*
  frontotemporal dementia, 1101–1102, 1102*f*
  progressive supranuclear palsy, 425*t*, 1102, 1105*t*, 1108
Taxanes, 411, 522*t*, 525, 617, 617*t*
Temozolomide, 482*t*, 492, 522*t*, 523*t*, 526
Temperature effects on nervous system, 665–667

Temporal arteritis, 420–421, 902. *See also* Giant cell arteritis (GCA)
Tenecteplase, 77
Teriflunomide, 593, 800
Teriparatide, 378, 621*t*, 625
Tetanospasmin, 861
Tetanus, 861–862
  hyperthermia and, 662*t*, 664
  neonatal, 589
  neuromuscular junction disorders and, 1075*t*
  in pregnancy, 589–590
  vaccine for, 861–862
Tetany
  in hypocalcemia, 279, 338, 380, 1019
  in hypokalemia, 278
  in hypomagnesemia, 280
Tetrabenazine, 608, 610, 612*t*, 1024, 1027–1028, 1030–1031, 1033, 1038–1039, 1039*t*, 1042
Tetrahydrocannabinol (THC), 185, 554, 644, 1011
Tetrahydrofolic acid (THEA), 238
Tetrathiomolybdate, 214
Thalassemia, 445
  neurologic manifestations of, 445
Thalidomide, 451, 737
  for leprosy, 737
  neurologic complications of, 451, 522*t*, 523*t*, 611, 617, 1039*t*, 1060*t*
Theophylline, 604, 605*t*, 611, 616, 970, 1014*t*, 1021, 1027*t*, 1039*t*, 1048*t*
Therapeutic hypothermia, 671
Therapeutic vaccination, 864
Thermoregulatory disorders
  environmental causes of, 664–665
    hyperthermia, 665
    hypothermia, 665
  heat exhaustion, 665
  heat stroke, 665, 667
  manifestations and management of, 667–671
  neurologic causes of, 662–663
    corpus callosum agenesis, 663–664
    degenerative diseases, 663
    effector pathways lesions, 663
    hypothalamic lesions, 662–663
    thermoregulatory system overload, 664
Thermoregulatory sweating
  impairment in, management of, 144–145
  tests of, 139–140, 139*f*, 140*f*, 232, 312
Thermoregulatory system
  description of, 661–662
  overload of, neurologic diseases that cause. *See* Malignant hyperthermia; Neuroleptic malignant syndrome; Serotonin syndrome
Thiamine, 209, 242, 670
Thiamine deficiency
  bariatric surgery and, 202
  beriberi and, 243–244, 1071–1072
  clinical manifestations of, 200, 202, 209, 242–244, 1071–1072
  diagnosis of, 236*t*, 244, 245*f*, 630
  dialysis and, 262–263
  etiology of, 242–243, 243*t*
  hyperemesis and, 596
  Korsakoff syndrome and, 244, 630–631
  and neuropathy, 634, 1071–1072
  treatment of, 236*t*, 244, 630
  vasogenic edema and, 244
  Wernicke encephalopathy and, 244, 262–263, 357*t*, 441, 629–630, 785–786
Thiamine pyrophosphate (TPP), 242
Thick-filament myosin loss, 998*t*, 1004–1005
Thimerosal, 857, 864
Thiopental, 40, 972, 986*t*, 987, 1036*t*
Thiotepa, 492, 523*t*, 530
Thoracic outlet syndrome, 1062, 1062*f*
Thrombocytopenia, 49, 59, 92–93, 108, 175, 180, 236, 349*t*, 356, 382–383, 442, 448, 451, 462–463, 467, 469, 500*t*, 605, 628, 635, 735, 751*t*, 793, 824, 877, 886*t*, 887. *See also* Thrombotic thrombocytopenic purpura (TTP)
  and intracranial hemorrhage, 92, 108, 349*t*, 448–449, 462–463, 605, 793
Thrombocytopenia-absent radius syndrome, 349*t*
Thrombolysis, 58, 77. *See also* Emergency reperfusion treatment
Thrombolytic therapy
  acute, 77
  ischemic stroke treated with, 95
Thrombomodulin, 177, 466, 471–472
Thrombophilia
  components of thrombophilia screening, 175, 175*t*
  hereditary, 177–178, 471–472
    activated protein C resistance. *See* Activated protein C (APC)
    antithrombin III deficiency, 471
    arterial thrombosis and, 473–474
    factor V Leiden, 472
    interactions between, 473
    protein C deficiency. *See* Protein C, deficiency of
    protein S deficiency. *See* Protein S, deficiency of
    prothrombin G:A 20210 mutation, 472
    stroke and, 177, 473–474
  neurocutaneous manifestations of, 349*t*
Thrombosis. *See also* Stroke
  antiphospholipid antibody-associated, 176, 469–471
  cerebral venous. *See* Cerebral venous sinus thrombosis (CVST)
  deep vein. *See* Deep vein thrombosis (DVT)
  systemic lupus erythematosus and, 469
Thrombotic thrombocytopenic purpura (TTP)
  characteristics of, 599–600
  description of, 357–358, 358*f*, 465–466
  in pregnancy, 599–600
Thrombus formation, 57
  prevention of, 47–48
Thymectomy, for myasthenia gravis, 430, 518, 973, 1076
Thymoma
  myasthenia gravis and, 430, 500–501, 518–519
  paraneoplastic cerebellar degeneration and, 510–511
Thyroid disease
  and headache, 1051
  hyperthyroidism. *See* Hyperthyroidism
  hypothyroidism. *See* Hypothyroidism
  multiple sclerosis and, 301
  seizures and, 1019
Thyroid eye disease. *See* Thyroid-associated ophthalmopathy
Thyroid storm, 298–299
Thyroid-associated ophthalmopathy, 296–298, 297*f*, 425*t*, 426*t*, 430
Thyroid-stimulating hormone, 332–333
Thyrotoxic myopathy, 292–293
Thyrotoxic periodic paralysis, 293–295, 1078
Thyrotoxicosis. *See* Hyperthyroidism
Tick-borne encephalitides, 746, 755
Tick-borne encephalitis virus, 742, 744*t*, 864

Tics, drug induced, 611
Tilt-table testing, 134
Tinel sign, 308, 495
Tinnitus, 289, 384, 400–401, 406, 408–413, 422–423, 442, 456, 527, 587, 599, 613–614, 648, 954–956, 970, 1025
Tissue plasminogen activator, 78–79
  ischemic stroke treated with, 95–96, 174, 468, 584
  lacunar syndromes treated with, 113
TNFRSR11 gene, 382–383
Tobacco and stroke, 184
Toll-like receptor (TLR) activation, 729
Toluene, 651, 1026
Tonic pupil, 434, 436
Topiramate, 255, 315, 321, 495, 572*t*, 583, 606, 609, 936, 1011, 1017, 1024, 1036*t*, 1039*t*, 1041, 1050–1053, 1053*t*
  dose adjustments for, 1010*t*
  hyperthermia and, 666*t*
  for parasomnias, 934*t*, 935
  pharmacokinetics of, 1009*t*
  during pregnancy, 579–582
Topotecan, 523*t*, 530
Torsades de pointes, 163–164, 168, 1049
Toscana virus, 742, 744*t*
Tourette syndrome, 323, 567, 592, 611, 1048
  during pregnancy, 592
Toxic encephalopathy, 298, 650–652, 655, 862, 981*t*. *See also specific toxins*
Toxic exposure
  postural hypotension caused by, 129–130
  in pregnancy, 591
Toxic neuropathy
  alcoholic, 634–635, 1072
  arsenic, 654–655, 1073
  lead, 653–654, 1073
  organic solvents and, 652
  organophosphate-induced, 657–658
  pyridoxine-induced, 1072
Toxins
  chorea and, 1025–1026, 1027*t*
  dystonia and, 1025–1026, 1027*t*
  myoclonus induced by, 1034–1037, 1036*t*
  parkinsonism and, 1042–1043
  sensory neuronopathy and, 1061, 1071–1073. *See also* Sensory neuronopathy
  tremors and, 1039–1040
Toxocara canis, 835–836
Toxocara catii, 835–836
Toxocara spp., 822*t*, 835–836
Toxoid vaccines, 854*t*, 855
Toxoplasma gondii, 790, 825, 825*f*
  abscesses caused by, 266–267, 1030, 1043–1044
  aseptic meningitis caused by, 748
  characteristics of, 822*t*
  chorioretinitis caused by, 825, 826*f*
  hosts of, 825
  prevalence of, 825
  transmission of, 1079
Toxoplasma infections, 796
Toxoplasmic encephalitis (TE), 826
Toxoplasmosis
  cerebral, 825–828, 826*f*
    asymptomatic, 825
    characteristics of, 776*t*
    congenital, 590, 825–826
    cranial imaging of, 826*f*, 827
    diagnosis of, 827
    in HIV-infected patients, 776*t*, 777–778, 777*f*, 778*f*, 827
    magnetic resonance imaging of, 826*f*, 827
    manifestations of, 822*t*, 825
    in pregnancy, 590, 827
    transmission of, 825
    treatment of, 778, 827
  myositis caused by, 1079
  ocular, 827
Tr antibody, 510
Tramadol, 315, 641, 967, 985, 987, 1014*t*, 1021, 1036*t*, 1068
  for restless legs syndrome, 932–933, 932*t*
Transcatheter aortic valve replacement (TAVR), 49–50
Transcranial Doppler (TCD) ultrasonography, 68–69
  for brain death determination, 1096–1097, 1097*f*
  for detecting vasospasm, 108
  in sickle cell anemia, 178
  stroke evaluations, 118
Transesophageal echocardiography (TEE), 47, 68–69, 71–72, 76–77
  valvular vegetations, 92, 95
Transforaminal anesthetic neural block, 959
Transient emboligenic aortoarteritis, 29
Transient erythroblastopenia of childhood, 442
Transient ischemic attack (TIA), 28, 50–51, 65–66, 79–80, 111, 115–116, 118, 132, 261, 350, 394, 442, 528, 584, 974, 976
  after radiation therapy, 535
  anemia and, 442
  antiphospholipid antibodies and, 584
  antiplatelet therapy and, 116
  aortic disease as cause of, 28–31, 118
  atherosclerosis as cause of, 28
  atlanto-occipital subluxation and, 391
  bevacizumab and, 528
  carotid artery stenosis and, 115–116
  cocaine and, 638
  dialysis and, 260–261
  endocarditis and, 350
  Fabry disease and, 267
  migraine versus, 1050
  neurosarcoidosis as cause of, 875
  polycythemia and, 456
  in pregnancy, 584
  preoperative considerations, 974, 976
  risk of, after carotid angiography, 959–960
  temporal arteritis and, 903
Transjugular intrahepatic portosystemic stent shunting, 192
Transplant recipients, seizures in, 1017–1018
Transplantation, 785–801. *See also* Organ transplantation; Post-transplantation period
  allogeneic, 791
  autologous, 791
  cardiac, 51–52
  conditioning regimen, 791
  fungal infection risks, 805
  graft types, 791
  and headache, 1052–1053
  hematopoietic cell transplantation (HCT), 791–793
    early complications, 791–792
    intermediate complications, 792
    late complications, 793
  immune reconstitution inflammatory syndrome (IRIS), 790
  immunosuppression for. *See* Immunosuppression
  infection risks, 791–792
  opportunistic infections after, 793
  peripheral nerve injuries during, 794–795
  renal, neurologic complications of, 264–267

    - brain tumors, 265–266, 265*f*, 266*f*
    - central nervous system infections, 266–267, 268*f*, 269*f*
    - femoral neuropathy, 264
    - non-Hodgkin lymphoma, 265
    - primary central nervous system lymphoma, 265–266, 266*f*
  - seizures after, 786–787, 1017–1018
  - solid organ transplantation (SOT), 793–797
    - cardiac transplantation, 795–796
    - hepatic transplantation, 793–795
    - pancreatic transplantation, 796
    - pulmonary transplantation, 796
    - renal transplantation, 795
    - small bowel and multivisceral transplantation, 796–797
  - stem cells, 791
  - syngeneic, 791
- Transposition of the great arteries (TGA), 53–54
  - balloon atrial septostomy in neonates with, 56
- Trans-sphenoidal surgery, 331–332, 586
- Transtentorial herniation, 9–10, 109, 1086–1088, 1094
- Transthoracic echocardiography (TTE), 58–59, 68–69, 92
- Transthyretin, 1071
- Transverse myelitis, 127, 228, 351, 460, 470, 514, 529, 755, 761–763, 763*t*, 789, 800, 848, 856*t*, 892–893, 906, 1029
- Trauma
  - barotrauma, 411
  - cerebral, and seizures, 1021–1022
  - orbital, 430–431
  - parkinsonism and, 1045
  - trochlear nerve palsy caused by, 429
- Traumatic aortic injury, 38
- Traumatic brain injury (TBI), 673. *See also* Concussion/mild traumatic brain injury (mTBI)
  - cardiac manifestations of, 166
  - postconsussion syndrome. *See* Postconcussion syndrome
  - seizures caused by, 1021
- Traumatic mononeuropathies, in pregnancy, 596
- Trematode infections
  - paragonimiasis, 837
  - schistosomiasis, 836–837
- Tremor, 1038–1041
  - calcineurin inhibitors and, 797
  - central oscillator, 1038
  - cerebellar, 1041
  - characteristics of, 1038
  - diagnosis of, 1041
  - drugs that cause, 611, 1038–1039, 1039*t*
  - flapping, 611
  - functional, 942–943
  - hemochromatosis and, 1040
  - HIV and, 1040
  - Holmes, 1041
  - hyperthyroidism and, 296
  - immune disorders and, 1041
  - infections and, 1040
  - intention, 1040
  - mechanical, 1038
  - metabolic disorders and, 1040
  - pathologic, 1038
  - physiologic, 1038
  - postural, 611
  - rest, 1038, 1041–1042
  - stroke and, 1038
  - treatment of, 1041
  - tuberculous meningitis and, 1044
  - uremic encephalopathy and, 253
  - Wilson disease and, 211, 1040
- *Treponema pallidum*, 180, 354, 704, 706–707, 748, 845, 1029*t*, 1059, 1103
  - *T. pallidum* particle agglutination assay (TPPA) test, 846
- Triazolam, for parasomnias, 919, 934*t*
- *Trichinella spiralis*, 834, 835*f*
- *Trichinella* spp., 822*t*, 834, 835*f*
- Trichinosis, 834, 1077*t*, 1079
- Trichloroethylene, 652
- Trichorrhexis nodosa, 367*t*
- Tricyclic antidepressants, 221, 1049, 1051–1052, 1053*t*
  - for cataplexy, 923
  - diplopia from, 615
  - gastroparesis from, 221
  - hallucinations and, 608
  - and headache, 1049, 1051
  - hypotension, postural, from, 311, 616
  - hypothermia and, 667*t*
  - intestinal dysmotility from, 221, 223
  - movement disorders from, 609, 611, 1026, 1029*t*, 1032, 1035, 1036*t*, 1038
  - neuropathy from, 1064*t*
  - overdose of, 1035
  - for pain, 315, 495, 572*t*, 595–596, 634, 752, 781, 783, 892, 1060–1061
  - seizures caused by, 606, 1020–1021
  - serotonin syndrome, 664
  - sexual dysfunction and, 572*t*, 616
  - thermoregulation abnormalities, 664, 666*t*, 667*t*
  - urinary retention, 616
- Trientine, 214
- Trigeminal neuralgia, 368, 385–386
  - in sarcoidosis, 872
  - in Sjögren syndrome, 892
- Trigeminal neuropathy
  - drug induced, 619
  - in Sjögren syndrome, 891
  - in systemic sclerosis, 893
- Trihexyphenidyl, 1026, 1027*t*, 1032, 1041
- Triosephosphate isomerase deficiency, 447
- Triptans, 183, 185, 404, 581, 604, 613, 666*t*, 969–970, 985, 1050, 1052, 1053*t*
  - hyperthermia and, 666*t*
- Trisomy, 21, 58
- Trochlear nerve palsy, 310–311, 425, 428–429, 700
- *Tropheryma whippelii*, 207, 433, 1037
- Tropical spastic paraparesis, 782, 847
- Tropical sprue, 209, 239
- Troponin, 70, 117, 159–160, 162–163, 166–167
- Trousseau sign, 338
- Trousseau syndrome, 500*t*
- Trousseau test, 279
- Truncal radicular neuropathies, 309–310
- *Trypanosoma brucei*, 828
- *Trypanosoma brucei gambiense*, 822*t*, 828
- *Trypanosoma brucei rhodesiense*, 822*t*, 828–829
- Trypanosomiasis, 828–829
- Tube feeding in dementia, 1105–1106, 1120
- Tuberculoid leprosy, 728–729, 730*t*, 731, 731*f*
- Tuberculomas, 722–723, 725, 844
- Tuberculosis
  - HIV and, 720
  - incidence of, 717
  - neurocutaneous manifestations of, 353*t*
  - otoneurologic manifestations of, 406–407
  - pathogenesis of, 717–718, 718*f*
  - pulmonary, 717

- Tuberculosis (*Continued*)
  - subpial, 718
  - treatment for, 723–725
- Tuberculous arachnoiditis, spinal, 722–723
  - antituberculous chemotherapy for, 723–724
  - diagnosis of, 723
  - signs and symptoms of, 723
  - treatment of, 723–725
- Tuberculous meningitis (TM), 180, 717–722
  - atypical features of, 719–720
  - bacteriology of, 721
  - cerebrospinal fluid examination, 720–721
  - characteristics of, 776*t*
  - in children, 718
  - chorea and, 1028
  - clinical presentation of, 719–720
  - communicating hydrocephalus in, 719
  - computed tomography of, 721
  - corticosteroids for, 724
  - diagnosis of, 720–722
  - differential diagnosis of, 722, 722*t*
  - dystonia and, 1028
  - HIV infection and, 720, 776*t*, 780–781
  - magnetic resonance imaging of, 721
  - neuroradiologic evaluation of, 721
  - nucleic acid amplification test, 721
  - parkinsonism and, 1044
  - pathogenesis of, 717–718, 718*f*
  - pathology of, 718–719
  - in pregnancy, 590
  - signs and symptoms of, 719, 719*t*
  - staging of, 719
  - and stroke, 179–180
  - treatment of, 723–725
- Tuberculous osteomyelitis, 388–389
- Tuberculous otitis media, 406–407
- Tuberous sclerosis, 74, 345–347, 346*f*
- Tumor necrosis factor-α
  - dexamethasone effects on, 690–691
  - granulomatous inflammation and, 882–883
  - inhibitors of
    - for ankylosing spondylitis, 390
    - inflammatory bowel disease, 205
    - inflammatory myopathies caused by, 621–622
    - optic neuritis caused by, 615
    - peripheral neuropathy caused by, 618
    - for relapsing polychondritis, 394
  - interleukin-1 and, 690
- Tumors, in pregnancy, 582–583
- Twitches, drug-induced, 624

U

- U waves, 164, 167
- Ubiquitin carboxylterminal esterase L1 (UCH-L1), 674–675
- Ulcerative colitis, 36*t*, 128, 204–206, 1016, 1092
- Ulnar nerve
  - compression of
    - perioperative, 983–984, 983*f*
    - in rheumatoid arthritis, 895–897
  - leprosy and, 733, 735–736
  - lesions of, dialysis and, 261–262, 1063
  - neuropathy, 309
- Uncal herniation, 427–428
- Undifferentiated connective tissue disease (UCTD), 857
- Uniform Determination of Death Act, 1095–1096
- Unresponsive wakefulness syndrome (UWS), 1097–1098
- Unruptured cerebral aneurysms, 106–107
- Upbeating nystagmus, 432
- Upper airway obstruction, 16
- Upper airway stimulation, sleep-related breathing disorders of, 927
- *URE1* gene, 806–807
- Uremic encephalopathy, 251–255. *See also* Dialysis; Dialysis disequilibrium syndrome; Renal disease; Renal transplantation
  - asterixis and, 252
  - cerebrospinal fluid findings in, 254
  - clinical features of, 252–253
  - convulsions, 255–257
  - electroencephalography findings in, 254, 255*f*
  - hormonal changes and, 252
  - indicators of, 252–253
  - investigations of, 253–255
  - laboratory studies, 253–254
  - metabolic abnormalities and, 252
  - myoclonus and, 252, 1034
  - parathyroid hormone and, 252
  - pathophysiology of, 252
  - seizures and, 253
  - treatment of, 255
  - tremulousness and, 253
- Uremic myopathy, 258, 1082
- Uremic neuropathy, 255–257, 1071
- Urge syndrome, 548
- Urgency-frequency syndrome, 548
- Urinary retention
  - description of, 546
  - differential diagnosis of, 547–548, 548*t*
  - Fowler syndrome and, 547–548
  - neurologic causes of, 547–548, 548*t*
  - sphincter electromyography evaluation, 552
- Urodynamic studies, 549–551
- Uroflowmetry, 549, 550*f*
- Urothelium, 542–544
- Uveomeningitis, 355
- Uveoparotid fever, 407

V

- Vaccine adverse event reporting system (VAERS), 855–856
  - neurologic disorders reported to, 856*t*
- Vaccine Safety Datalink, 856, 862
- Vaccine(s)
  - adjuvants and preservatives, 856–857
  - adverse events of, detection of, 855–856
  - attenuated, 854
  - complications of, 855
  - component, 855
  - conjugate, 855
  - diphtheria, 860
  - diphtheria, pertussis, and tetanus, 860–862
  - DNA, 855
  - emerging viruses, 863–864
  - hepatitis B, 863
  - historical background, 853–854
  - immune responses to, 855
  - inactivated, 854
  - influenza, 862–863
  - measles, mumps, rubella, 858–860
  - mechanism of action, 854*t*
  - pertussis, 860–861
  - pneumococcal, 855, 856*t*

  poliomyelitis, 863
  potential neurologic complications of, 864*t*
  Sabin, 863
  Salk poliovirus, 854, 854*t*
  Shingrix, 857
  smallpox, 857–858
  subunit, 854–855
  tetanus, 861–862
  therapeutic, 864
  toxoid, 855
  types of, 854–855
  varicella, 854, 854*t*, 856*t*
  vector, 855
  web sites of, 857*t*
Vacuolar myelopathy, in HIV-infected patients, 781, 783
Vagal nerve stimulation therapy, 579
Vagus nerve, 158. *See also* Recurrent laryngeal nerve palsy
  cardiovagal function tests, 134–135
  diabetes mellitus and, 229
  heart rate responses regulated by, 126, 134–135
  Lewy bodies and, 226
  in sarcoidosis, 872
  sexual dysfunction and, 569
Valacyclovir
  for herpes simplex virus meningitis, 748, 751*t*
  for varicella zoster virus encephalitis, 752
Valbenazine, 579, 610, 1024, 1031, 1033
Valganciclovir, for cytomegalovirus meningitis, 780
Valosin-containing protein gene, 386
Valproic acid, 606, 787
  after organ transplantation, 786–787, 1017
  for chorea, 1028
  fetal syndrome from, 579
  hematologic complications, 461
  hepatic complications and contraindications, 1010–1011, 1017
  in HIV-infected patients, 769–770
  hyperandrogenism caused by, 321–322
  hypothermia and, 667*t*
  for Kleine-Levin syndrome, 924
  lupus and, 1016
  myoclonus and, 1035–1037, 1036*t*
  neurologic complications of, 606, 611, 1029*t*
  for pain, 495
  pharmacokinetics of, 1009*t*
  porphyria and, 1017
  during pregnancy, 321, 579, 582
  for seizures, in renal failure, 255, 1010–1011, 1010*t*
  for status epilepticus, 1012
  tremor induced by, 1038
Valsalva maneuver, 73, 732
  baroreceptor reflex sensitivity, 135–137
  cardiovascular response to, 135, 136*f*
  definition of, 135
  recording of, 135, 136*f*
  syncope caused by, 133
Valve endocarditis
  native, anticoagulation in, 96
  prosthetic, anticoagulation in, 96
Valve replacement, surgical, 50
  stroke after, 50
Valvular atrial fibrillation, 76, 173
Valvular diseases, cardiac, 75–76
  aortic valve stenosis, 76
  lambl excrescences, 76
  mitral annular calcification, 75
  mitral valve prolapse, 75
  mitral valve regurgitation, 75
  mitral valve stenosis and rheumatic heart disease, 76
  prosthetic heart valves, 76
Vancomycin, 388, 410
  for bacterial meningitis, 684, 688–690, 688*t*, 689*t*, 692
  brain abscess and, 695, 695*t*
  ototoxicity, 410, 613–614
  spinal epidural abscess and, 699
  subdural empyema and, 697
Vanilloids, 555
Variant Creutzfeldt–Jakob disease, 759
Varicella zoster virus (VZV), 686, 788–789
  central nervous system invasion by, 752–753
  characteristics of, 741, 743*t*, 751–752
  cutaneous zoster (shingles), 752
  encephalitis caused by, 752–753
  herpes zoster oticus caused by, 406
  in immunocompromised patients, 757
  meningitis caused by, 746
  neurocutaneous manifestations of, 353*t*, 752
Variegate porphyria, 357*t*, 358–359, 1017, 1040, 1073
Variola vaccine. *See* Smallpox vaccine
Variolation, 853, 858
Vascular dementia, 313–314, 470, 768*t*, 1100–1101, 1103, 1105*t*
Vascular disorders and obstructive sleep apnea, 18
Vascular endothelial growth factor, 450, 456, 476, 528
Vascular headaches, 575, 604
Vascular imaging for patients with infective endocarditis, 94–95
Vasculitic neuropathy, 501*t*, 515, 517, 898–902, 1058*t*, 1065–1068, 1066*t*
Vasculitis, 718–719, 898. *See also individual disorders*
  Behçet syndrome. *See* Behçet syndrome
  central nervous system, 393
  herpes zoster-related, 1040
  myocardial infarction risks, 904
  nonsystemic vasculitic neuropathy, 899–900
  polymyalgia rheumatica, 902–904
  polymyalgia rheumatica (PMR) and giant-cell arteritis, 902–904
  primary, 899–900
  in relapsing polychondritis, 393
  systemic, 900–901
  Takayasu arteritis, 904
  temporal arteritis, 420–421, 902
Vasoconstricting agents, hyperthermia and, 666*t*
Vasoconstriction in acute hypertension, 102
Vasodilating agents, hypothermia and, 667*t*
Vasogenic edema, 197, 244, 268*f*, 477–479, 477*f*, 492, 531*t*, 584, 629–630, 668, 691*f*, 778*f*
  dexamethasone for, 479
  hypertensive encephalopathy and, 121. *See also* Posterior reversible encephalopathy syndrome (PRES)
  thiamine deficiency and, 244, 629–630
Vasogenic erectile dysfunction, 564
Vasopressin
  cardiovascular responses associated with, 130
  osmotic pressure effects on, 130
Vasopressin receptor antagonists, 336
Vasospasm, 66, 107–108, 167–168, 185, 274–275, 639, 964
Vasovagal response, 956
Vasovagal syncope, 133, 144, 956
Vector vaccines, 855
Vecuronium, 1001–1002
Vegetative state, persistent, 1033, 1097–1098, 1117
Vemurafenib, 481, 482*t*, 492, 522*t*, 523*t*

- Venereal disease research laboratory (VDRL), 180, 704, 846, 1030, 1103
- Venezuelan equine encephalitis, 687, 743*t*
- Venoarterial (VA) ECMO, 48
  - ischemic stroke in, 49
- Venoarteriolar axon reflex, 126
- VENOST study of Cerebral Venous Thrombosis, 471
- Venous thrombosis
  - cerebral. *See* Cerebral venous sinus thrombosis (CVST)
  - intracranial, in pregnancy, 585
  - risk factors for, 471
- Venous–venous bypass procedure, 795
- Venovenous (VV) ECMO, 48
- Ventral respiratory group (VRG), 4
- Ventricle, left, 74–75
  - acute myocardial infarction, 74
  - cardiomyopathies, 74–75
  - left ventricular dysfunction, 75
- Ventricular arrhythmias, 83, 165, 670–671, 1012
- Ventricular tachycardia, 83, 158, 671
- Ventriculoperitoneal shunt, 423, 533, 817–818, 953, 1104
- Verapamil, 108, 331*t*, 612*t*, 620*t*, 1008, 1012, 1027*t*, 1042, 1049
- Vertebral artery
  - anatomy of, 28, 33*f*
  - intimal dissection of, ischemic complications of, 960
  - stroke, 904
- Vertebral fractures, 374, 378, 390, 392
- Vertebral osteomyelitis, 387–389, 388*f*
- Vertebrobasilar insufficiency, 384, 405
- Vertebroplasty, 378
- Vertigo, benign paroxysmal positional, 401, 403*f*, 432
- Vestibular neuronitis, 401
- Vestibular nystagmus
  - central, 432
  - peripheral, 431
- Vestibular schwannoma, 401
- Vestibular/Ocular Motor Screening (VOMS) Assessment, 676
- Vestibulotoxicity, 613
- Videocystometry, 550–551
- Vigabatrin, 255, 321, 606, 608–609, 611, 614, 1010–1011, 1010*t*, 1036*t*, 1039*t*
- Vincristine, 306*t*, 451, 458, 466, 522*t*, 523*t*, 525–526, 526*t*, 612*t*, 614, 617, 1039*t*, 1064*t*, 1077*t*
- Vinorelbine, 482*t*, 522*t*, 525
- Viral encephalitis
  - approach to, 758–759
  - arthropod-borne viruses and, 754–755
  - cerebral edema in, 759
  - description of, 748–759
  - enteroviruses and, 756
  - Epstein–Barr virus and, 756–757
  - global incidence of, 749
  - herpes simplex virus and, 749–751
  - in immunocompromised patients, 757
  - lymphocytic chorio-meningitis virus and, 756
  - progressive multifocal leukoencephalopathy (PML) and, 267, 269*f*, 451, 500*t*, 523, 606, 741, 757–758, 758*f*, 772, 775–777, 776*t*, 780, 789, 789*f*, 847, 1018, 1030, 1044, 1091
  - rabies virus and, 755–756
  - recovery from, 759
  - seizures in, 759
  - signs and symptoms of, 749*t*, 758–759
  - treatment of, 759
  - varicella zoster virus and, 751–753
  - West Nile virus and, 753–754, 753*f*, 754*f*
- Viral envelope proteins, 855
- Viral etiologies, of chronic meningitis, 847–850
- Viral infections
  - central nervous system
    - acute hemorrhagic leukoencephalitis, 762
    - encephalitis. *See* Viral encephalitis
    - meningitis. *See* Viral meningitis
    - pathogenesis of, 741–742
    - postinfectious complications of, 761–763
    - postinfectious encephalomyelitis, 761–762, 762*f*, 763*t*
    - transverse myelitis, 762, 763*t*
  - host response to, 742
  - movement disorders and, 1030
  - in post-transplantation period, 788–789
  - types of, 741
- Viral meningitis, 686. *See also* Aseptic meningitis
  - antiviral agents for, 748, 751*t*
  - approach to, 747–748
  - arthropod-borne agents that cause, 746
  - causative agents of, 742, 746*t*
  - cerebrospinal fluid examination for, 748
  - clinical presentation of, 742
  - Colorado tick fever virus and, 743*t*, 746
  - diagnosis of, 747
  - enteroviruses and, 742
  - headache in, 742
  - herpes simplex virus type 2 and, 742, 746
  - HIV and, 747
  - hospitalizations caused by, 742
  - imaging and, 748
  - laboratory tests, 748
  - lumbar puncture for, 747
  - lymphocytic chorio-meningitis virus and, 743*t*, 746–747
  - mumps virus and, 743*t*, 747
  - prevalence of, 742
  - prognosis for, 748
  - signs and symptoms of, 746*t*
  - treatment of, 748
  - varicella zoster virus and, 742, 746
- Viral myositis, 1078–1079
- Virchow–Robin spaces, 779, 869–870, 870*f*, 874
- "Virus-like" particles (VLPs), 855
- Visceral larval migrans, 835–836
- Visual disorders, drug-induced, 614
  - pupillary changes, 614
  - refractive changes, 614
- Visual evoked potentials, 289, 298, 417, 878
- Visual loss
  - chemotherapeutic agents and, 523*t*
  - in cryptococcal meningitis, 817
  - functional, 943
  - paraneoplastic syndromes and, 513
  - postoperative, 984
  - retrochiasmal, 423–424
  - in temporal arteritis, 903
- Vitamin A deficiency, 246–247
  - clinical manifestations, 246
  - diagnosis, 247
  - etiology, 246
  - treatment, 247
- Vitamin B_1 deficiency. *See* Thiamine deficiency
- Vitamin B_3 deficiency, 246
- Vitamin B_6. *See* Pyridoxine, deficiency of
- Vitamin B_{12} deficiency, 202, 206, 209–210, 236–237, 442, 590, 1034, 1072
  - Alzheimer disease and, 1103

- bariatric surgery and, 202
- clinical manifestations of, 237, 366*t*, 1072
- cobalamin screening in, 238
- dementia and, 1100*t*, 1103
- diagnosis of, 236*t*, 238, 442
- in elderly, 237
- encephalopathy and, 443
- etiology of, 236–237, 442
- eye movement disorders and, 443–444
- functional, 443
- Imerslund–Graesbeck syndrome and, 444
- infantile, 444
- myelopathy and, 206, 443
- myoclonus and, 1034
- neurologic complications of, 442–443
- neuropsychiatric manifestations of, 237
- nitrous oxide and, 236*t*, 237, 444
- optic neuropathy and, 237, 443
- peripheral neuropathy and, 443, 1063*t*, 1064*t*, 1072
- postural hypotension secondary to, 128
- in pregnancy, 590
- prevalence of, 236
- risk factors for, 237*t*
- sensory neuropathy and, 443
- signs and symptoms of, 237
- subacute combined degeneration, 236
- subclinical, 443
- treatment of, 236*t*, 238–240

- Vitamin D
  - deficiency of, 247
    - clinical manifestations, 247
    - description of, 279–280
    - diagnosis, 247
    - etiology, 247
    - osteomalacia caused by, 379–380, 1077
    - treatment, 247
  - dietary sources of, 379–380
  - functions of, 380
  - immune system and, 380
- Vitamin E deficiency, 208, 241–242, 1072
  - clinical manifestations of, 242
  - diagnosis of, 236*t*, 242
  - etiology of, 242
  - polyneuropathy and, 1072
  - treatment of, 236*t*, 242
- Vitamin K antagonists, 76, 79–80, 177
- Vitamin K deficiency, 92–93, 462, 472
- Vitamin K_1, 579–580
- Vocal cord weakness, 11, 237, 495, 925
- Vogt–Koyanagi–Harada syndrome, 353*t*
- Voice disorder, 943
- Voiding
  - central mediation of, 542
  - dysfunction of, 553–554
- Volatile anesthetics, 988, 1002
- Voluntary euthanasia, 1112
- Voluntary respiratory control, disorders of, 9
- von Hippel–Lindau disease, 269, 270*f*, 456
- von Recklinghausen disease, 344, 461
- von Willebrand factor (VWF), 358, 461, 465–466
- Voodoo death, 160
- Voriconazole, 617*t*, 618, 620, 792, 811, 818, 843
- Voxel-based morphometry and functional movement disorders, 944
- Voxelotor, 444–445

W

- Wakefulness, ascending arousal system and, 915
- Waldenström macroglobulinemia, 445–446, 449, 451–452, 506*t*, 517, 1041, 1064*t*, 1071
- Wallenberg syndrome, 404
  - Horner syndrome and, 435
  - postural hypotension in, 127
- Warfarin, 77, 173, 976
  - for atrial fibrillation, 76, 78–80, 78*t*, 114, 259, 468
  - for intracranial venous thrombosis, 586
  - in perioperative period, 976
  - regional anesthesia and, 983
  - stroke risk reduction using, 78, 114, 118, 173, 176, 584
  - for systemic lupus erythematosus, 890, 1030
- Warfarin versus Aspirin in Reduced Ejection Fraction (WARCEF) trial, 75, 80
- Warfarin vs Aspirin Recurrent Stroke Study (WARSS), 470
- Weakness. *See individual disorders*
- Wegener granulomatosis, 1065–1066. *See also* Granulomatosis with polyangiitis (GPA)
  - description of, 368, 394, 407
  - otitis media and, 407, 407*t*
  - otoneurologic manifestations of, 407
- Weight loss, for obstructive sleep apnea, 927
- Werdnig-Hoffman disease, 13
- Werner syndrome, 367*t*
- Wernicke encephalopathy, 244, 628*f*, 629–630, 785, 786*f*. *See also* Thiamine deficiency
  - description of, 193, 202, 209, 262–263
  - diagnosis of, 244, 629–630
  - dialysis and, 262–263
  - hepatic encephalopathy and, 193, 196
  - hypothermia and, 662, 663*t*, 670
  - imaging and, 196, 245*f*, 786*f*
  - infection and, 670
  - Korsakoff syndrome and, 244, 357*t*, 596, 631
  - malabsorption associated with, 202, 207, 209
  - malnutrition and, 202, 411, 500*t*, 630
  - neuropathologic findings, 630
  - ocular palsies and, 429
  - organ transplantation and, 785–786
  - otoneurologic manifestations of, 411, 432
  - pancreatitis and, 200
  - postural hypotension secondary to, 127
  - pregnancy and, 596
  - prognosis for, 630
  - thiamine deficiency and, 243–244
  - treatment of, 630
- West Nile virus, 687
  - anterior horn cell disease and, 13, 1059
  - characteristics of infection, 753–754
  - description of, 267, 687
  - encephalitis caused by, 742, 743*t*, 753–754, 753*f*, 754*f*
  - encephalomyelitis, 13
  - flaccid paralysis caused by, 753–754, 1059
  - incidence of, 750*f*, 753–754, 753*f*, 754*f*
  - manifestations of, 1059
  - meningitis caused by, 742, 743*t*
  - movement disorders and, 1037
  - rash and, 685
  - in transplant recipients, 788*t*, 793
- Whipple disease, 207–208, 207*t*, 224, 433, 1029*t*, 1037
- Whole-brain radiotherapy, 480, 480*t*
- Williams syndrome, 58
- Wilson disease, 211, 240, 322–323, 1010

Wilson disease (*Continued*)
  cerebellar dysfunction and, 212
  clinical presentation of, 211, 1026, 1032, 1034, 1040, 1043
  diagnosis of, 213, 241
  dystonia secondary to copper accumulation in, 1026
  gait abnormalities and, 212
  hepatic manifestations of, 211, 793
  Kayser–Fleischer rings, 212, 212*f*
  laboratory diagnosis, 241
  liver failure and, 211
  movement disorders and, 1026, 1032, 1034, 1040, 1043
  neurologic manifestations of, 211–212
  ophthalmologic manifestations of, 212, 212*f*
  osteoporosis and, 212–213
  pathophysiology of, 211
  in pregnancy, 591–592
  psychiatric manifestations of, 212
  renal impairment and, 212–213
  sex hormones and, 322–323
  sexual activity in, 567
  treatment of, 213–214, 241
  tremor and, 211, 1040
Winterbottom sign, 828–829
Wiskott–Aldrich syndrome, 463
Withdrawal
  alcohol. *See* Alcohol withdrawal
  opiate, 642
  sedative-hypnotic, 641
Withdrawal symptoms and maternal epilepsy, 580
Wolff–Parkinson–White syndrome, 83
Women's health and stroke, 173–175
  menopause, 175
  pregnancy, stroke in, 174–175
Wound botulism, 642, 1074
Wrist, median neuropathy at, 140, 210, 261, 291, 308, 595, 1064–1065, 1068. *See also* Carpal tunnel syndrome

X
Xanthochromia, 107
Xanthopsia, 615
Xeroderma pigmentosa, 347, 366*t*
Xylohypha bantiana, 811
Xyrem. *See* Sodium oxybate

Y
Yawning, 10
Yersinia pestis, 353*t*
Yo antibody, 416*t*, 510, 1041, 1059, 1071
Yohimbine, 144, 573

Z
Zaleplon
  for insomnia, 919
Zeitgebers, 914
Zic4 antibodies, 510–511
Zidovudine, 589, 622, 771*t*, 782, 1077*t*, 1078, 1083, 1083*t*
Zika virus, 755
Zimeldine, 619
ZNF592 gene, 871
Zolendronic acid, 384
Zolmitriptan, 1050
Zolpidem, 641, 1118–1119
  for insomnia, 919
  for parasomnias, 934*t*
  for persistent vegetative state, 1118–1119
  for restless legs syndrome, 932*t*
Zonisamide, 321, 579, 1010*t*, 1033–1034
  hyperthermia and, 666*t*
  serum concentration, 578
Zoster sine herpete, 752
Zygomycetes, 804*t*

AMINOFF'S NEUROLOGY AND GENERAL MEDICINE

SIXTH EDITION

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Aminoff's Neurology and General Medicine, 6th Edition is the standard and classic reference providing comprehensive coverage of the relationship between clinical neurology and general medicine. It defines both the neurologic aspects of general medical disorders and the general medical and other implications of various neurologic diseases. The book provides an account of clinical neurology from a different perspective and serves as an interface between neurology and the other medical specialties. Patients with neurologic disorders are often complex and inevitably have other coexisting disorders. Furthermore, many medical disorders have neurologic complications or manifestations. General medical disorders, in turn, are influenced by neurologic disease and their treatment may have neurologic consequences.

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